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# The American Heart Journal

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### Original Communications



### Department of Clinical Reports



### Department of Reviews and Abstracts




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# The American Heart Journal

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## Original Communications

### EFFECT ON THE CIRCULATION OF MECHANICAL OCCLUSION OF INDIVIDUAL ARTERIES OF THE EXTREMITIES; RELATION TO ARTERIAL EMBOLISM*


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IN MANY cases of sudden arterial occlusion resulting from embolism or thrombosis the temperature of the skin of the distal parts of the affected extremity decreases sharply to that of the room or to a temperature approaching that of the room. Gangrene supervenes in about 50 per cent of cases.[1] In sharp contrast to this incidence of gangrene is that following simple ligation. Halsted[2] in 1912 reviewed the reports of ligation of the common iliac artery and found the incidence of gangrene to be about 6 per cent. In 1924[3] he reviewed reports of cases in which the subclavian artery had been ligated and failed to find any evidence that gangrene had been caused by uncomplicated ligation or ligations of either subclavian artery.

Mulvihill, Harvey, and Doroszka[4] reviewed reports of sixty-nine ligations of the common iliac, external iliac, common femoral, and superficial femoral arteries in the period from 1900 to 1930 and found an incidence of gangrene of only 14.7 per cent. In only half of these cases was the gangrene extensive enough to necessitate amputation. Mulvihill and Harvey,[5] in experimental studies on dogs, found that while the incidence of gangrene was small following ligation of the external iliac arteries, the temperatures of the feet were reduced to the level of that of the room in from two to six hours and returned to normal within a variable period of several more hours.

It has been shown that mechanical occlusion of the brachial or femoral artery of human subjects causes a decrease in the temperature of the skin which, however, is not half as fast or as great as if circulation to the arm or leg were arrested by means of a pneumatic cuff. However, it is a common observation in many instances of arterial embolism, which is at least


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no more than occlusion of an artery, that there is almost immediate cessation of circulation similar to compression of the limb by a pneumatic cuff. Pain occurs in most instances of arterial embolism, yet according to Seifert,[6] ligation of an artery is usually not followed by the type of pain that is observed in arterial embolism.

It was with the hope that some explanation might be found for the comparatively high incidence of gangrene and pain subsequent to arterial embolism, as contrasted with their low incidence following arterial ligation, that this study was undertaken.

## METHOD OF STUDY

The subjects used in this study had no demonstrable impairment of circulation to the extremities. Studies were conducted with the patients lying in a room, the temperature of which was constant and sufficiently less than that of the limbs so that decreases in the temperature of the limbs could occur. The patients lay in the room for half an hour before the studies were begun to obviate any effects of sudden changes in the temperature of the environmental air and any effect of activity on the temperature of their extremities. Temperatures of the skin of the great toes and of the index fingers were determined in studies on the legs and arms, respectively, by an electric thermometer at the beginning of the test and at five-minute intervals thereafter until ten minutes after pressure on the artery was released. In each test the comparable digit of the opposite extremity was used as a control. Arteries were occluded by a mechanical device that gave a localized area of pressure over the artery to be studied. In all instances except those in which the popliteal and femoral arteries were occluded there was compression of the tissues opposite the rubber pad which occluded the arteries by a metal pad which was a part of the compression device. Absence of the distal pulse was considered indicative of complete occlusion of the artery. This was checked repeatedly to prevent errors arising from slipping of the clamp allowing reestablishment of circulation in the artery.

There was no visible evidence of venous congestion in any of the studies except when the femoral and brachial arteries were occluded. In each test in which the femoral artery was occluded cyanosis and distention of veins were noted. This occurred in only two tests in which the brachial artery was occluded. Obstruction of the veins may have prevented somewhat a decrease in the temperature of the skin in these studies, but this is improbable, as Mulvihill, Harvey, and Doroszka[4] have shown that ligation of the companion vein did not influence a change in temperature resulting from ligation of the external iliac artery of dogs.

In the present studies observations were made following occlusion of the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries.

## RESULTS

*Occlusion of Brachial Artery.*—The brachial artery was occluded above the elbow for thirty minutes in five cases. In none of these cases was there any pain or discomfort except at the site of application of the clamp. In all cases there was a decrease in the temperature of the skin, which varied from 1.5° to 5.0° C. Release of compression caused a rapid increase in the temperature of the skin in only three cases, in two of which the temperature ten minutes after removal of the obstruction exceeded the temperature at the beginning of the test.

The composite graph of these five cases shows a moderate and gradual decrease in temperature while the artery was compressed and evidence of hyperemia after release of the compression (Fig. 1). In two cases the temperature of the control digit diminished in about the same degree as did that of the digit of the extremity of which the artery was occluded; in the remaining three cases there was no significant change in the temperature of the control digit. Study of individual charts used to make this composite graph shows that in all cases except one there was no further decrease in temperature after compression had been maintained for twenty-five minutes, and that in but one case did the temperature of the skin decrease to that of the environmental air, which was 24° C.

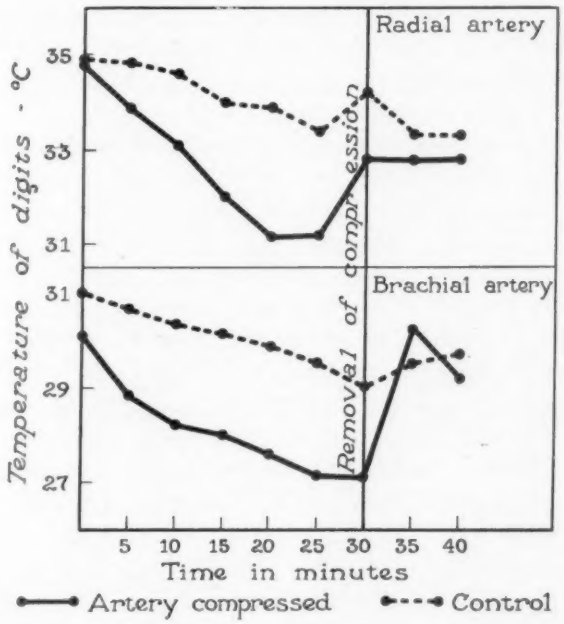


Fig. 1.—Effects produced on temperature of the skin of the digits by occlusion caused by mechanical compression of the radial and brachial arteries.

In the other cases the temperature of the skin did not decrease further, although it was 2°, 4°, 6°, and 8° C., respectively, greater than that of the room.

*Occlusion of Ulnar Artery.*—The ulnar artery was compressed at the wrist in three cases. No significant change in the temperature of the skin of the digit occurred. No unusual symptoms were noted.

*Occlusion of Radial Artery.*—The radial artery was occluded at the wrist in four cases. In no case was there any pain or distress except at the site of compression. The decrease in the temperature of the digit varied from 2.2° C. to 7.0° C. In three cases the temperature increased again in spite of maintained compression of the artery at periods varying

from fifteen to twenty-five minutes after compression was begun. In no case was the minimal temperature of the digit as low as that of the room; it failed by 2.0° C., 4.4° C., 2.2° C., and 9.0° C., respectively, to diminish to that of the room. In three cases the temperature of the control digit decreased somewhat less than that of the digit of the limb whose artery was compressed, and in one case it actually increased. The composite graph of these four cases indicates a gradual decrease of temperature until twenty minutes after the application of compression, then an increase in temperature which was quite marked before compression was removed (Fig. 1).

*Occlusion of Femoral Artery.*—The femoral artery was compressed just below the inguinal ligament in five cases. In all cases there was a moderate decrease in temperature which varied from 4° C. to 1° C. Venous congestion of the limb was marked in all cases, apparently because of occlusion of the accompanying femoral vein. This venous congestion caused a feeling of fullness in the limb within ten to fifteen minutes after compression, and in three cases this became so uncomfortable in twenty to twenty-five minutes that the test had to be discontinued. Subsequent to release of the compression there was a prompt increase in the temperature of the skin in three cases. The graph (Fig. 2) represents the results of study of these five cases for the first twenty minutes, of four cases for twenty-five minutes, and of two cases for thirty minutes. That part of the graph indicating determination of the temperature of the skin following removal of compression is a composite of the results in all five cases. The temperature of the skin failed to decrease to that of the room by 3.0° C., 2.1° C., 1.6° C., and 0.4° C., respectively, in four cases; in one case the temperature decreased to that of the room, which was 26.5° C. It should be emphasized, however, that the temperatures were still decreasing in all instances when the tests were terminated.

*Occlusion of Popliteal Artery.*—The popliteal artery was occluded in the popliteal space in three cases, and in all cases there was a prompt drop in peripheral skin temperatures (Fig. 2). Numbness began to develop in from fifteen to twenty minutes, and soon the patient stated that the distal part of the limb felt as though it were dead. This may have been due to compression of the peroneal nerve. Release of the obstruction caused a prompt increase in temperature in all but one case. In an additional test not included in Fig. 2 the subject slept. As a result, the temperature of the control digit increased 6° C., but that of the digit of the limb in which the popliteal artery was occluded remained stationary. Although the minimal temperature resulting from obstruction of the popliteal artery was not as low as that of the room by 5.2° C., 2.0° C., and 1.5° C., respectively, it should be emphasized that it was still decreasing when the tests were terminated.

*Occlusion of Posterior Tibial Artery.*—The posterior tibial artery was occluded at the ankle in five cases. In two of the cases there was no

change in the temperature of the skin. In the three remaining cases the temperature diminished from 1.5° C. in one case to 4.0° C. in another. In all instances the decline in temperature had stopped before the compression was removed. The composite graph of these five cases indicates a gradual but small decrease in the temperature and an increase following removal of compression (Fig. 2). The minimal temperatures resulting from occlusion of the artery failed to reach that of the room by

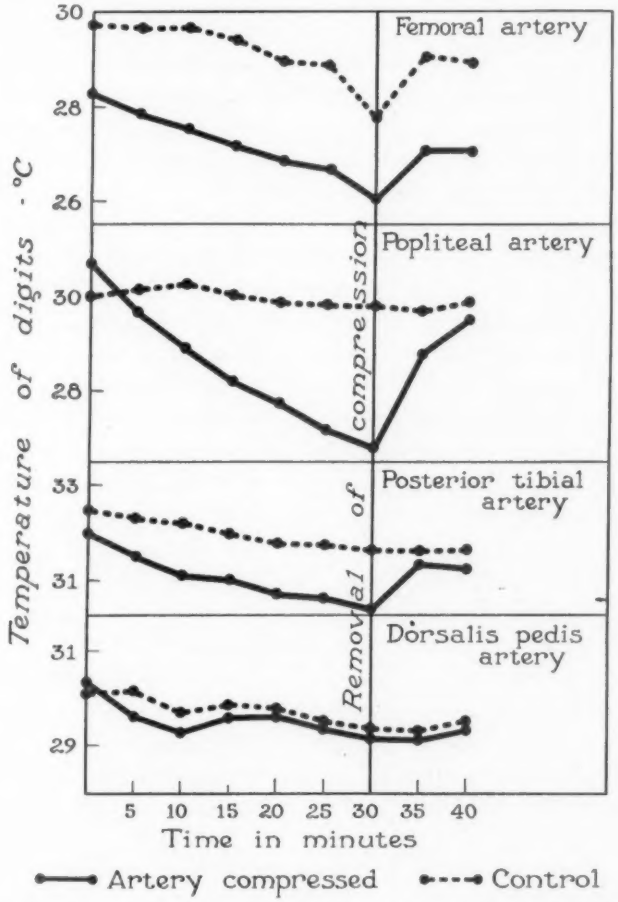


Fig. 2.—Effects on temperature of the skin of the digits produced by occlusion caused by mechanical compression of the femoral, popliteal, posterior tibial, and dorsalis pedis arteries.

3.0° C., 0.7° C., and 2.6° C., respectively, in the three cases in which the temperature was influenced by the procedure.

*Occlusion of Dorsalis Pedis Artery.*—The dorsalis pedis artery was occluded over the dorsum of the foot in five cases. In four cases there was a decrease in temperature varying from 1.4° C. in one case to 4.0° C. in another. In two of these cases there was an increase in temperature before compression was removed, which was temporary in one case but

which persisted in another case until the obstruction was removed. In the fifth case there was actually an increase in the temperature while compression was applied. The composite graph of these tests shows a minimal decrease in the temperature but is slightly misleading since it includes the results of study of the case in which there was actually a rise in temperature (Fig. 2).

## SUMMARY OF RESULTS

These studies indicate that mechanical occlusion of identical arteries of different individuals produces varying results on the circulation. This seems attributable to the variability of function of identical arteries of different individuals. Compression of the ulnar artery produced no effect on circulation to the index finger as determined by calculation of the temperature of the skin. Compression of the dorsalis pedis and posterior tibial arteries individually caused reduction of the circulation in only a minor degree. These arteries individually appear, therefore, to be of minimal importance in maintaining circulation to the acral parts. Mechanical compression of the brachial artery caused reduction of the temperature of the skin to an average of 27.0° C. in an environmental temperature considerably lower than this in about twenty-five minutes, following which there was ordinarily no further reduction in temperature. Compression of the radial artery caused a reduction of the temperature of the skin to an average of about 31.0° C. in about twenty minutes, following which there was ordinarily no further reduction. The arteries of the upper extremity, in order of their importance in maintaining circulation, are therefore the brachial, radial, and ulnar. Compression of the femoral artery caused a decrease of the temperature of the skin of the great toe to an average of 26.0° C. and that of the popliteal to an average of about 27° C. In both instances the temperature of the toes was still decreasing at the end of thirty minutes of compression. In the lower extremity, therefore, the femoral artery appears somewhat more important than the popliteal artery in maintaining circulation to the foot, while the dorsalis pedis and posterior tibial arteries individually are of very minor importance.

## COMMENT

These studies appear to have considerable importance in understanding some of the events in arterial embolism. It appears from our studies that occlusion by mechanical compression of the main arteries of the extremities for periods until there is no further diminution in circulation as a result of the compression does not produce pain except the distress produced by pressure at the site of occlusion and except occlusion of the femoral and popliteal arteries in which studies distress seemed to be produced by venous occlusion and pressure on the peroneal nerve respectively. In no instance was there simulation of severe pain ob-

served in embolism. This is strange since occlusion of these arteries by an embolus is frequently attended by much pain. Apparently, however, as Lewis[7] has pointed out, the pain of arterial embolism does not occur coincidentally to lodgment of the embolus but results from ischemia produced by embolism. This contention is supported by our observations as mechanical occlusion, which produces the same effect on an artery, so far as circulation through it is concerned as embolism does, does not produce pain simulating that due to embolism. In this connection it is of some interest to note that slow occlusion of arteries, such as that which occurs in thromboangiitis obliterans or arteriosclerosis obliterans, does not produce pain ordinarily, being comparable in this regard to arterial compression. It is quite apparent, therefore, that pain in arterial embolism is not due to mere mechanical obstruction of the artery by the embolus. If it were true that embolism were nothing more than arterial occlusion, it would be uniformly painless, as is compression of an artery.

In a similar manner our studies indicate that the diminution of circulation in arterial embolism is not due entirely to mere mechanical obstruction of an artery, since the effects of embolism on the circulation frequently exceed greatly those of simple obstruction of an artery or ligation of it.[1-4] If this were not true, embolic obstruction of the dorsalis pedis, posterior tibial, or ulnar arteries would produce no grossly detectable effect on circulation. Also, embolic occlusion of the brachial and radial arteries would produce only minor impairment of the circulation.

There appears to be an additional factor in arterial embolism which accounts for pain and the diminution of circulation which is absent following simple ligation or compression of an artery. This seems to be diffuse arterial spasm.* Arterial spasm in embolism is known to exist, for it has actually been seen by Seifert,[6] by Gosset, Bertrand, and Patel[8] and by others. Its presence has been demonstrated indirectly by observations that papaverine hydrochloride, which is a vasodilator, may cause remarkable reestablishment of circulation within a short period after embolism.[6, 9] Good results have also been reported by Herrmann and Reid[10] following use of intermittent suction and pressure, which effects vasodilation. Also, the circulation of many extremities, which is greatly reduced shortly after embolism, may spontaneously return to a nearly normal level. In all cases of embolism in which there is recovery of circulation after an original marked decrease in it, the embolus, that is, arterial occlusion, has remained unchanged yet circulation improves and pain disappears. It is customary to attribute this to increased circulation through collateral arteries not influenced primarily by embolism. However, in view of our present studies on arterial compression it ap-

*If Lewis' contentions are correct, arterial spasm only causes pain indirectly by producing ischemia.

pears that these arteries are abnormally spastic as a result of embolism, since were this not true marked diminution in circulation would be absent in cases of peripheral arterial embolism. The variation in pain and circulatory disturbances resulting from roughly similar instances of embolism and the variability of recovery are, in all probability, manifestations of the degree and persistence of spasm in arteries not directly occluded by emboli as well as of the importance to circulation of the artery occluded.

## CONCLUSIONS

Simple arterial compression produces effects dissimilar to those of arterial embolism in that pain observed in embolism is absent and the effect of such compression on circulation is usually not great. This dissimilarity appears to be attributable to arterial spasm in embolism and its absence in simple arterial compression.

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# AN APPROACH TO THE DIAGNOSIS OF CONGENITAL HEART DISEASE*

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THE attitude toward congenital heart disease is changing. It is becoming more generally recognized that in a goodly number of cases the correct approach will lead to a correct anatomical diagnosis clinically. Because of the prominence of the physical signs, congenital cardiac anomalies seldom escape detection for long, but too often an erroneous prognostic significance is attached to these signs. Frequently enough to demand attention, an individual with a congenital cardiac anomaly dies at an advanced age from causes perhaps unrelated to the murmur for which his activities had been restricted since childhood. Then there is the other side of the picture, represented by the sudden death of an individual who had been in apparently robust health, as a result of paradoxical embolism, or again, by the development of subacute bacterial endocarditis in an individual whose bicuspid pulmonic valve had hitherto not given rise to a single sign or symptom. Quite a proportion of congenital cardiac defects are, of course, of such a nature as to be either entirely incompatible with life or permit only a short and crippled existence.

It therefore becomes increasingly interesting, and in view of the wide differences in prognosis with regard to various congenital lesions, very important to differentiate them, not only from one another, but also from acquired cardiac disease. What, then, is the approach to the clinical recognition of these entities? Their clinical recognition depends on: (1) an understanding of the ontogenesis of each of these anomalies, (2) an understanding of the physiological alterations imposed on the cardiovascular system by their presence, and (3) the correct interpretation of groups of findings which form in many cases a syndrome characteristic, or at least extremely suggestive, of a particular anomalous arrangement.

## THE GENESIS OF CARDIOVASCULAR ANOMALIES

If one begins with the premise that the cardiovascular system recapitulates its ancestral history during the course of its own development, it is reasonable to expect that, if arrest of development does occur, it will represent the adult form of one of the lower vertebrate series, dependent on the stage at which arrest takes place. The intermediate stages are, in fact, particularly well illustrated in the develop-

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ing mammalian heart because it assumes functional activity at a very early stage of gestation. As in its phylogenetic history, it starts as a simple tubelike structure with the same subdivisions as the adult fish heart (Fig. 1, *a*). Expressed in the simplest form its development from then on consists essentially in: (1) septal formations dividing the auricle, the ventricle, the bulbus cordis, and the common aorta or truncus arteriosus each into two sections (Fig. 1, *b*); (2) torsion of the cardiac tube; (3) development of the bulbus cordis; (4) the incorporation of the sinus venosus into the right auricle (Fig. 1, *b*); (5) the evolution of the aortic arches, some being obliterated, others becoming the permanent aortic arch, pulmonary artery and their branches, and (6) closure of fetal channels after birth.

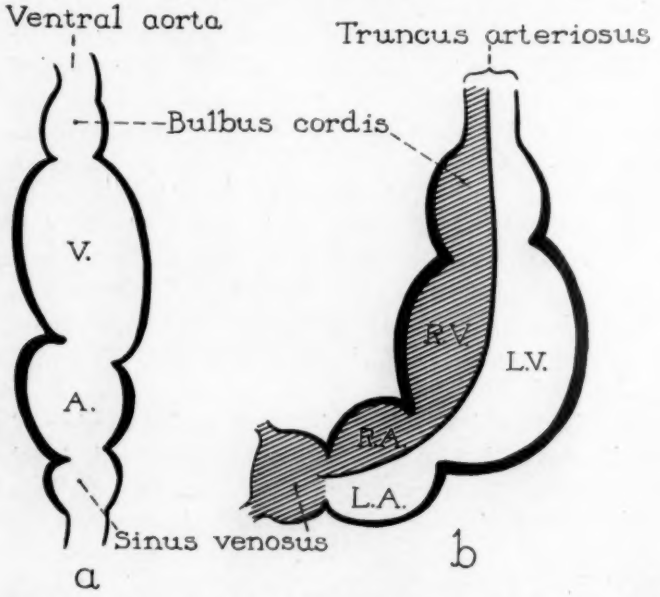


**Fig. 1*a*.—Fish type of heart, which is similar to the heart in the fourth-week human embryo; *b*, septal formation: The sinus venosus is incorporated in the right auricle, the bulbus cordis becomes part of the right ventricle (mainly) and of the left ventricle, and a clockwise rotation occurs in the bulboventricular part of the cardiac tube.**

*Septal Formations.*—This process is the physiological response on the part of the cardiac tube to the evolution of a lung-respiratory system so that the venous and arterial systems eventually become completely separated from one another. Any of these septal formations may be incomplete, resulting in any one of a variety of well-known defects (Table I). The cor biloculare in which no septa have developed is the replica of the fish heart. The amphibian form is represented by the cor triloculare biatriatum in which the interventricular septum is absent. Small interventricular septal defects, such as the maladie de Roger, resemble the adult form of the heart of some of the higher reptiles.

Now if it is realized that the different developmental processes which are being described are occurring more or less synchronously, it is apparent that multiple sites are liable to be involved, though isolated anomalies, of course, frequently occur. Normally, septal formations are complete after the seventh week of fetal life.

*Torsion of the Cardiac Tube.*—At an early stage the cardiac tube becomes kinked on itself by virtue of the fact that its extremities are relatively fixed as the primitive heart elongates (Fig. 1, *b*). The torsion to which I refer, however, applies to a clockwise rotation of the

TABLE I

CLASSIFICATION OF CONGENITAL HEART DISEASE

I. Anomalies associated with septal formation:
   1. Cor biloculare
   2. Cor triloculare biatriatum
   3. Cor triloculare biventriculare
   4. Auricular septal defects
   5. Ventricular septal defects
   6. Persistent truncus arteriosus

II. Anomalies associated with torsion of the cardiac tube and

III. Anomalies associated with development of the bulbus cordis:
   1. Subaortic stenosis
   2. Pulmonary stenosis
   3. Transposition of great vessels
   4. Tetralogy of Fallot
   5. Eisenmenger's complex
   6. Anomalies of the aortic and pulmonic valve cusps

IV. Anomalies associated with development of the aortic arches:
   1. Persistent right aortic arch with isthmus stenosis of the left arch
   2. Double aortic arches
   3. Coarctation of the aorta
   4. Anomalous origin of vessels arising from the aortic arch
   5. Patent ductus botalli

V. Dextrocardia

VI. Anomalies of the coronary vessels

bulboventricular end of the cardiac tube during which the aorta moves toward the left and partially behind the commencement of the pulmonary artery. If one will examine the anterior aspect of the adult normal heart this relationship will become clear. This torsion is necessary in order to bring the left ventricle into juxtaposition with that part of the truncus arteriosus which is destined to become the aorta, and the right ventricle into juxtaposition with the pulmonary artery. As in the adult heart of certain reptiles, there is a transitory stage in the human heart in which there are two aortae connected with the left ventricle, each with two cusps. In the process of torsion, the right aorta is obliterated whereas the left remains open to become the outflow chamber of the left ventricle. If this process of torsion is arrested, the aorta is left in a dextroposed position, in which case the right aorta persists instead of the left, or the right and left aortae may fuse

to form a large aortic trunk. In either case this dextroposed aorta, instead of bearing the normal relationship to the left ventricle, overrides the interventricular septum (which is usually incomplete) and the right ventricle (Fig. 2). In other words, the great vessels (the aorta and pulmonary artery) are transposed, and this transposition may be present in varying degrees depending on the degree of torsion that has occurred. Sometimes there is a small niche in the right ventricle which represents the obliterated right aorta. It is extremely likely that other developmental defects will accompany such a gross deviation from the normal, such as imperfect septal formations and incomplete evolution of the bulbus cordis.

Here, then, one sees the genesis of one of the important and interesting anomalies representing arrest at the reptilian stage, namely, the tetralogy of Fallot. This consists of dextroposition of the aorta, with an interventricular septal defect, pulmonary stenosis, and an hyper-

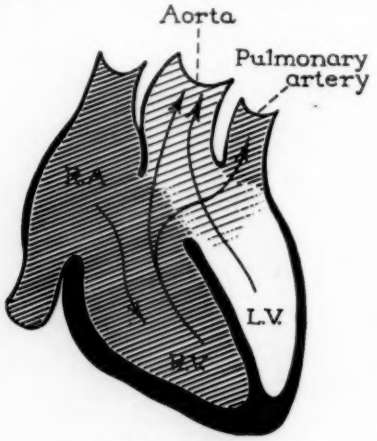


Fig. 2.—The tetralogy of Fallot, showing a large aorta which is dextroposed and overrides the interventricular septum. The latter is incomplete. The pulmonary artery is stenosed and the right ventricle is hypertrophied. The left auricle is not indicated in this diagram.

trophied right ventricle. Cusp anomalies are frequently associated with the tetralogy, especially in the form of bicuspid leaflets which are, interestingly enough, the normal for the reptilian species.

*The Development of the Bulbus Cordis.*—Essentially this consists of the incorporation of the major portion of the bulbus into the right ventricle, to form the conus arteriosus, and a smaller portion into the left ventricle. If this process is incomplete, the corresponding ventricle will be constricted or stenosed in that region. Thus in the case of the left ventricle there will be a stenotic band below the aortic valve, that is, a subaortic stenosis. Its counterpart in the right ventricle consists of a subpulmonic or infundibular stenosis.

In the genesis of some of the stenotic congenital lesions, fetal inflammatory processes probably play a part.

*The Incorporation of the Sinus Venosus into the Right Auricle.*—In the adult heart the sinus venosus is represented by that part of the right auricle which receives the blood from the superior and inferior venae cavae anatomically known as the sinus venarum.

*The Development of the Aortic Arches.*—Briefly stated, there are six pairs of aortic arches connecting the primitive ascending aorta to the primitive descending aorta. They are not all present at the same time. The left fourth arch becomes the aortic arch. The right fourth arch forms the innominate artery and the beginning of the right subclavian artery. The sixth arch gives origin to the pulmonary artery, and on the left side, to the ductus botalli.

The chief anomalous developments met are persistence of both fourth arches and persistence of the right arch in place of the left. The latter arrangement is closely related to coarctation of the aorta. The very

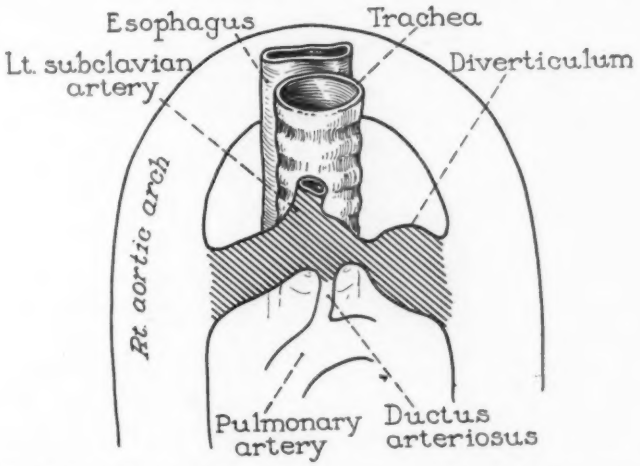


Fig. 3.—Persistent right aortic arch, representing the right fourth aortic arch. Note its relation to the trachea and esophagus. The shaded part represents the left fourth arch which normally becomes the aortic arch.

plausible explanation has been given that if for any reason the left fourth arch becomes stenosed, then one of two terminations results, namely, coarctation, or the right fourth arch may remain patent, forming the aortic arch.[1] In the latter instance the patency of the right arch is salutary; it usually runs over the right bronchus and behind the trachea and esophagus to join the descending aorta. The left arch is here represented by the left subclavian artery, the stenosed fourth arch and a diverticulum which would have formed that part of the aortic arch between the point where the ductus botalli joins it and the descending aorta if the left arch had been normally patent (Fig. 3). Coarctation of the aorta is frequently associated with aneurysms of the circle of Willis.[2, 3] Permanent patency of the ductus arteriosus (botalli) should be considered together with anomalies of the aortic arches, as the former is derived embryologically from the latter. The

opening up of the pulmonary circulation after birth usually leads to gradual closure of the ductus. Should conditions remain such that pressure in the pulmonic circuit and the aortic arch remains the same as before birth, the duct will remain patent. Patency of the ductus is frequently associated with other anomalies of the aortic arches.

*Closure of Fetal Channels.*—This refers to the closure of the ductus arteriosus and the foramen ovale.

*Classification.*—Associated with each of these processes, anomalous developments may occur and congenital cardiac lesions conveniently classify themselves under the corresponding subdivisions shown in Table I. Such a classification is self-explanatory and easily remembered. Viewed in this light, the corresponding physiological disturbance caused by each anomalous condition is readily understood and the symptoms and physical findings are more readily explained. There is, therefore, no particular advantage in dividing them into clinical groups.

## CERTAIN FACTS AND FINDINGS WHICH SHOULD LEAD ONE TO SUSPECT THE PRESENCE OF A CONGENITAL CARDIAC ANOMALY

*Bruits Not Explainable on the Basis of the Conventional Acquired Valvular Lesions.*—These have usually been noted in infancy and are rather constant over a period of years. The point of maximal intensity should be noted as well as the direction in which the murmurs are propagated.

*Thrills.*—These are frequently present over the areas of maximal intensity of the bruits, and both bruits and thrills become more readily elicited clinically after exercise.

*Evidence of Venous-Arterial Shunt, With the Usual Manifestations: Cyanosis, Polycythemia, and Clubbed Fingers and Toes.*—The group of cases in which the venous-arterial shunt is transitory, depending on temporarily induced increased pressure on the venous side, frequently have a history of episodes of dyspnea or cyanosis. A rather unique feature relative to the cyanosis of congenital heart disease is the absence of edema when the cyanosis is quite pronounced.

*Any Unusual Heart Contour in the Roentgenogram, Such as a Prominent Pulmonary Artery.*—Points readily overlooked are: lack of prominence of the aortic knob; shadows to the right of the sternum running up toward the right sternoclavicular joint, as is seen in persistent right aortic arch, and erosion of ribs, which may in itself be diagnostic of coarctation of the aorta. These features are often better elicited by fluoroscopy.

*Hypertension.*—In a young individual hypertension should lead one to examine the strength of the pulsation in the abdominal aorta and femoral arteries and to look for other evidence to exclude or confirm the presence of coarctation of the aorta.

*Congenital Anomalies.*—Congenital anomalies in any part of the body should lead one to examine carefully for cardiac anomalies. In Ab-

bott's series,[4] 18.8 per cent of patients had anomalies elsewhere. Mongolian idiots, too, are prone to have congenital cardiac lesions.

*Subacute Bacterial Endocarditis.*—This frequently occurs as a complication of congenital heart disease.

*Comment.*—Once an anatomical diagnosis has been arrived at, the resultant physiological disturbance should be reasoned out and examination should be made to see if the physical findings fit the case. There will in many instances be room for differences of opinion in the interpretation of physical signs, but it is only by making a concerted effort to establish a detailed diagnosis in each instance that one is going to become more expert in recognizing them.

## THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE

If one can divorce from one's mind the idea that congenital heart disease is an entity separate from heart disease in general and adheres to the physical principles governing electrocardiography, the subject becomes much more clearly understood. With the single exception of dextrocardia with complete situs transversus, there are no diagnostic electrocardiographic patterns in congenital anomalies. The information so obtained serves merely as one link in the chain of evidence.

Again I must refer to the physiological alterations concerned in any particular anomaly. If the condition is such as to throw added strain on the left ventricle, as in coarctation of the aorta or subaortic stenosis, a left axis deviation in the electrocardiogram will reflect such a condition as eloquently as it does in arterial hypertension or in acquired aortic disease. If myocardial changes result as a consequence, T-wave changes in Leads I and II can be expected to follow.[5] It so happens that the majority of congenital defects are attended sooner or later by strain on the right side of the heart, either because of arteriovenous shunts or stenotic pulmonary effects. Corresponding roughly to the degree, there will be right axis deviation and perhaps T-wave alterations in Leads II and III.[5] P-waves may be exaggerated, as in acquired mitral stenosis, indicating greater auricular activity.

Conduction interferences are at times of considerable diagnostic help when caused by interventricular septal defects, while coronary types of T-wave changes have been noted when the coronary vessels originated from the pulmonary artery.[6]

Auricular fibrillation is very unusual except in a widely patent foramen ovale accompanied by distention of the right auricle.

Very meager information is forthcoming from the literature regarding the fourth lead in cases of congenital heart disease. In the past year a clinical diagnosis of congenital heart disease was made in forty-three cases. A fourth lead (Wolferth) was recorded in seventeen cases. The frequency of abnormal changes is indicated in Table II. It is apparent again that such changes are not in any sense diagnostic but

TABLE II

A RECORD OF FOURTH LEADS IN CASES OF CONGENITAL HEART DISEASE

| CASE | AGE YR. | CLINICAL DIAGNOSIS | AXIS DEVIATION | FOURTH LEAD (WOLFERTH) | CARDIAC SYMPTOMS | COMMENT |
|---|---|---|---|---|---|---|
| 1 | 22? | Auricular septal defect and mitral stenosis | Marked R. V. P.* | Upright T-wave Absent R-wave | Early decompensation with cyanosis and clubbing | Exaggerated $P_2$ and $P_3$ waves |
| 2 | 45 | Patent ductus arteriosus and patent interventricular septum | R. V. P. (despite the presence of a superimposed hypertension) | Diphasic T-wave Absent Q-wave | Decompensation | Exaggerated $P_2$ and $P_3$; diphasic $T_2$ and $T_3$; delayed A-V conduction |
| 3 | 22 | Auricular septal defect and patent ductus arteriosus | Marked R. V. P. | Upright T-wave | Early decompensation | Exaggerated $P_2$ and $P_3$ |
| 4 | 41 | Patent ductus arteriosus with mitral and aortic endocarditis | R. V. P. | Upright T-wave with elevated R-T segment | Early decompensation | Auricular fibrillation |
| 5 | 27 | Patent ductus arteriosus | R. V. P. | Diphasic T-wave | Absent | |
| 6 | 37 | Patent ductus arteriosus | R. V. P. | Normal | Absent | |
| 7 | 16 | Ventricular septal defect | No preponderance | Normal | Absent | |
| 8 | 61 | Patent ductus arteriosus | R. V. P. | Normal | Absent | |
| 9 | 45? | Ventricular septal defect | No preponderance | Normal | Absent | |
| 10 | 23 | Patent ductus arteriosus | No preponderance | Normal | Absent | |
| 11 | 25 | Ventricular septal defect | No preponderance | Normal | Absent | |
| 12 | 52 | Auricular septal defect with mitral stenosis | R. V. P. | Isoelectric T-wave | Decompensation | Auricular fibrillation |
| 13 | 24 | Patent ductus arteriosus | R. V. P. | Normal | Absent | |
| 14 | 20 | Ventricular septal defect with patent ductus arteriosus | R. V. P. | Huge inverted T-wave | Poor cardiac reserve | Inverted $T_2$ and $T_3$; incomplete bundle-branch block; auricular fibrillation |
| 15 | 19 | Patent ductus arteriosus with ventricular septal defect | R. V. P. | Slight depression of R-T segment | Dyspnea on exertion | |
| 16 | 27 | Patent ductus arteriosus | No preponderance | Normal | Absent | |
| 17 | 19 | Ventricular septal defect and probable patulous foramen ovale | Marked R. V. P. | Deeply inverted T-wave. "M" notching of QRS with diminished Q and exaggerated S-wave | Dyspnea on exertion. Cyanosis and clubbing present | Exaggerated $P_2$. Incomplete bundle-branch block. Inverted $T_2$ and $T_3$. |

*Right ventricular preponderance.

seem to be associated with a cardiac mechanism which throws an added strain on the right side of the heart, particularly if the strain is pronounced or of long standing.

A group of twenty-six cases reported by Edeiken, Wolferth, and Wood,[7] in which the fourth lead showed the only electrocardiographic abnormality, included one congenital anomaly. The fourth lead was upright in this case and it was associated with right ventricular preponderance to the extent of +128°.

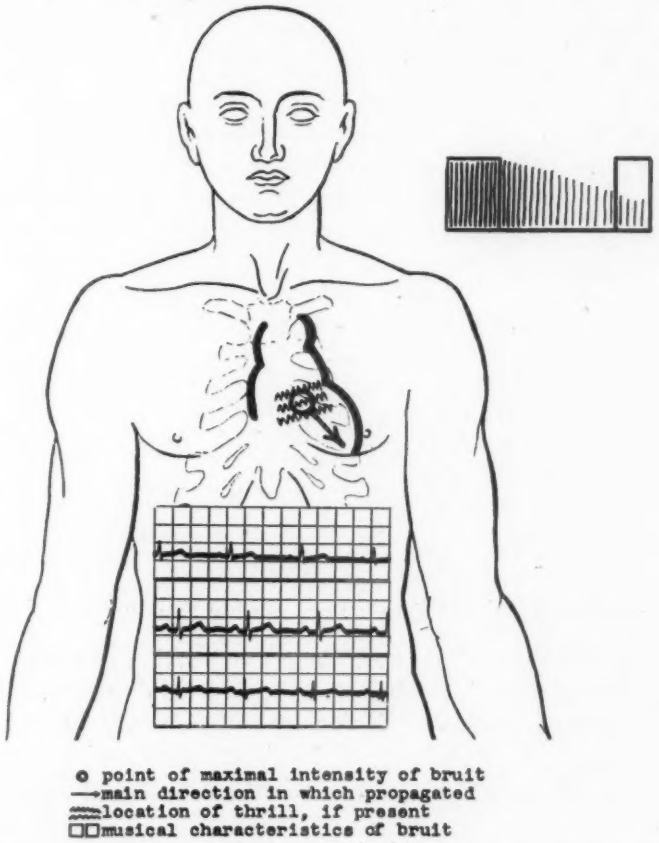


Fig. 4.—Interventricular septal defect; the heart contour is normal and the electrocardiogram is normal.

## THE DIAGNOSTIC FEATURES OF INDIVIDUAL CONGENITAL ANOMALIES

*Interventricular Septal Defect (Maladie de Roger).*—Mechanism. There is an arteriovenous shunt because of the higher pressure in the left ventricle. With a failing left ventricle, or with increased pressure on the right side of the heart, the flow is reversed and under these conditions only does cyanosis occur.

The syndrome (Fig 4). The bruit and the thrill are the important findings. Roger's original description[8] of the bruit was as follows:

"This murmur is uncomplicated by other murmurs; it begins with systole and is prolonged to such an extent that it entirely covers the natural tic-tac of the normal heart sounds." The heart's shape is usually normal, as is the electrocardiogram. Occasionally, however, there is evidence of interference with the conductive system. Symptoms are absent, but subacute bacterial endocarditis is a frequent complication.

*Interauricular Septal Defect (Widely Patent Foramen Ovale).*—Mechanism. The shunt again is arteriovenous until conditions arise which cause a reversal of pressures. Cyanosis is thus a frequent terminal event.

The syndrome. Until such events as just described occur, there are generally no signs or symptoms, no cardiac enlargement or abnormal contour features, and the condition may thus remain unsuspected and undiagnosed. A patent foramen ovale should be suspected when (1) there is a history of cyanotic spells or undue cyanosis during pulmonary infections, and (2) when systolic or presystolic bruits, with or

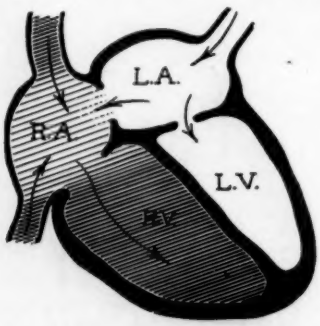


Fig. 5.—Lutembacher's disease (patulous foramen ovale with mitral stenosis).

without thrills, are audible over the upper portion of the sternum and are not otherwise explainable. When symptoms do occur, there is usually evidence of right ventricular hypertrophy with enlargement of the pulmonary artery and also of the right auricle. The roentgenologic and electrocardiographic findings will then be in keeping with such events.

Comment. Among congenital heart lesions, a widely patent foramen ovale is the only one which at times terminates in auricular fibrillation. Paradoxical embolism may occur, but subacute bacterial endocarditis is a rare complication.

*Lutembacher's Disease (Mitral Stenosis and Interauricular Septal Defect).*—Mechanism. Something of a vicious circle is created by the fact that an easier egress exists through the interauricular septal defect for the blood in the left auricle than through the stenosed mitral orifice (Fig. 5). This means that blood already aërated reaches the right side of the heart, to be sent to the lungs again. While this is no special disadvantage at first, the right ventricle soon hypertrophies,

and when it fails, as it inevitably does, a reversal of blood eventually results from the right side of the heart to the left, and cyanosis develops. As decompensation is controlled the degree of cyanosis decreases.

The syndrome. The syndrome consists of: (1) the auscultatory findings of mitral stenosis at the apex, (2) at times, a high-pitched bruit audible over the upper portion of the sternum accompanied by a thrill (in a recent case the correct diagnosis was arrived at by this finding),

Fig. 6.—Roentgenologic appearance of Lutembacher's disease, showing the enormous dilatation of the pulmonary vessels (simulating a mediastinal tumor) and the rounded apex, representing a much hypertrophied right ventricle.

(3) roentgenologic evidence of cardiac hypertrophy, especially affecting the right ventricle, a prominent pulmonary conus and an enlarged right auricle; the aortic knob is smaller than normal, and the pulmonary vessels may be so increased in prominence as to simulate pathologic mediastinal lymph nodes (Fig. 6) (in the case just referred to the preliminary diagnosis was mitral stenosis and Hodgkin's disease), and (4) marked right axis deviation in the electrocardiogram.

Comment. Right heart failure eventually results.

*Subaortic Stenosis.*—Mechanism. The mechanism is the same as in acquired aortic stenosis.

The syndrome. The syndrome consists of: (1) a harsh systolic bruit at the base transmitted to the vessels in the neck, (2) an accompanying thrill, (3) forceful action of the left ventricle in contrast to a weak radial pulse, (4) absence of symptoms, and (5) evidence of left ventricular strain roentgenologically as well as electrocardiographically (Fig. 7).

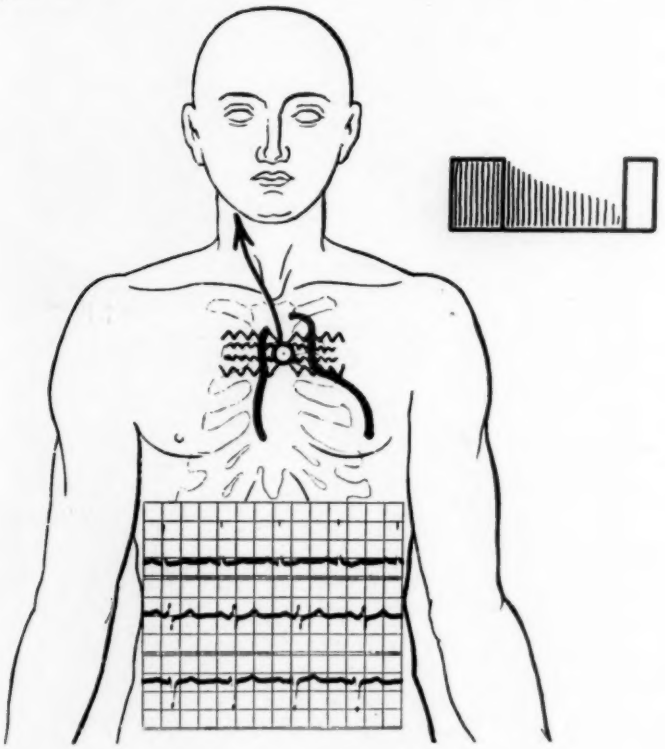


Fig. 7.—Subaortic stenosis. The left ventricle is hypertrophied and the electrocardiogram shows left axis deviation.

Comment. The prognosis is good.

*Pulmonary Stenosis.*—Mechanism. 1. With a closed interventricular septum, the right ventricle naturally hypertrophies markedly. Depending on the degree of the defect, cyanosis almost inevitably supervenes, although the individual may reach adult life before it becomes noticeable. Once it begins, it is likely to be progressive, with increasing clubbing and polycythemia. 2. With an interventricular septal defect (which is far more common), the load is taken off the right

ventricle to some extent, but cyanosis occurs earlier because of the venous-arterial shunt. In both instances the foramen ovale is likely to be patent, no doubt because of increased pressure on the right side of the heart; this may add to the venous-arterial shunt.

The syndrome. The syndrome consists of: (1) A harsh systolic bruit in the second left interspace, which is transmitted toward the left shoulder and not to the vessels in the neck, (2) a well-marked thrill, (3) a prominent conus, which is evidence of hypertrophy of the right

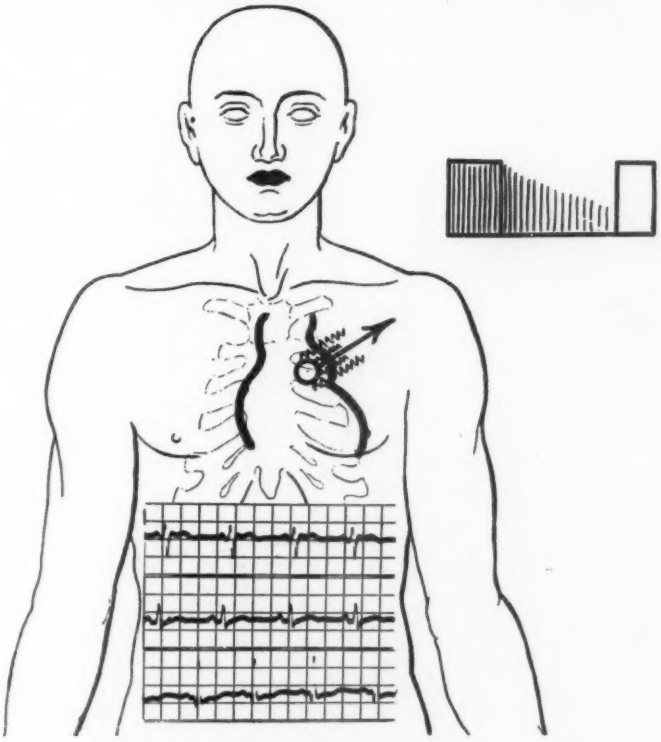


Fig. 8.—Pulmonary stenosis, showing the prominence of the conus shadow and the hypertrophied right ventricle. The electrocardiogram shows right axis deviation. The shading of the lips indicates cyanosis.

ventricle, and enlargement of the right auricle, (4) right ventricular strain electrocardiographically, and there may be T-wave changes in Leads II and III significant of right heart strain, and (5) cyanosis, sooner or later, with the usual secondary manifestations (Fig. 8).

Comment. Symptoms tend to develop early. Dyspnea on exertion heralds the manifestations associated with impaired oxygenation and myocardial damage. Not a few patients succumb to subacute bacterial endocarditis.

*The Tetralogy of Fallot.*—Mechanism. As the right ventricle empties itself, the smaller portion of venous blood enters the much narrowed pulmonary artery, whereas the major portion enters the large aorta which usually directly overrides the defect in the interventricular septum (Fig. 2). The venous blood which does get aërated returns to the left auricle and so to the left ventricle. With contraction of the latter, this aërated blood joins the stream of venous blood from the right ventricle in the aorta. It is apparent, then, that with the com-

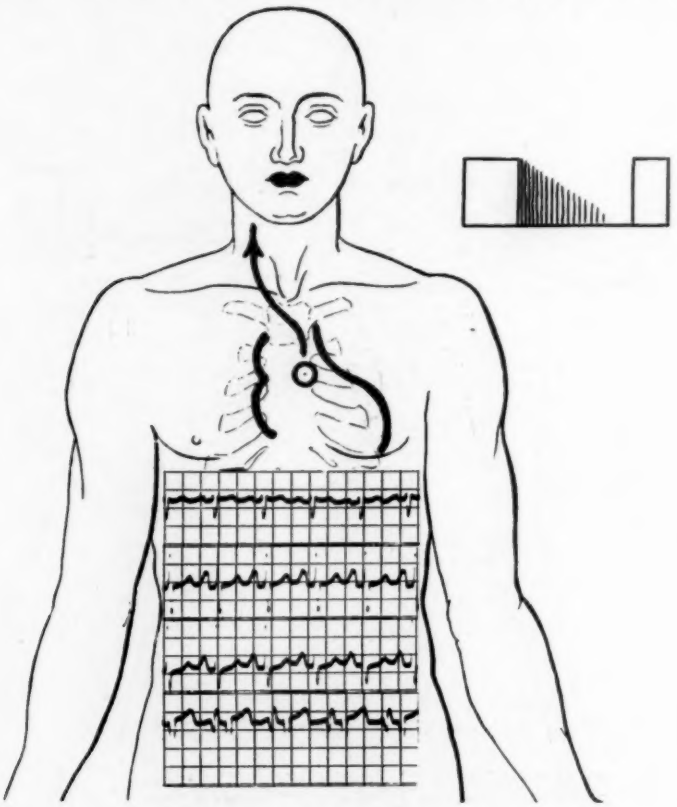


Fig. 9.—The tetralogy of Fallot: Note the boot-shaped heart, the right axis deviation in the electrocardiogram, with a positive T-wave in the fourth lead (Wolferth). The shading of the lips indicates cyanosis.

bined effects of the venous-arterial shunt and the much restricted pulmonary circulation, cyanosis will be prominent. The peribronchial vessels help, to a greater or lesser degree, to carry blood for aëration to the lungs, and the efficiency of this alternate route does a good deal toward establishing the prognosis in the individual case.

The syndrome. The syndrome is as follows: (1) Cyanosis tends to begin early in life and often becomes extreme, (2) bruits may be

absent, but there is usually a systolic murmur at the base transmitted to the vessels in the neck, with or without an accompanying thrill, (3) the heart becomes sabot-shaped because of the prominent right ventricle without enlargement of the pulmonary artery, and because of the dextroposition of the aorta, the great vessels will be prominent on the right, and (4) there is electrocardiographic evidence of right ventricular strain (Fig. 9).

*Patent Ductus Arteriosus.*—Mechanism. Because of the higher aortic pressure, blood is shunted from the aorta into the pulmonary artery.

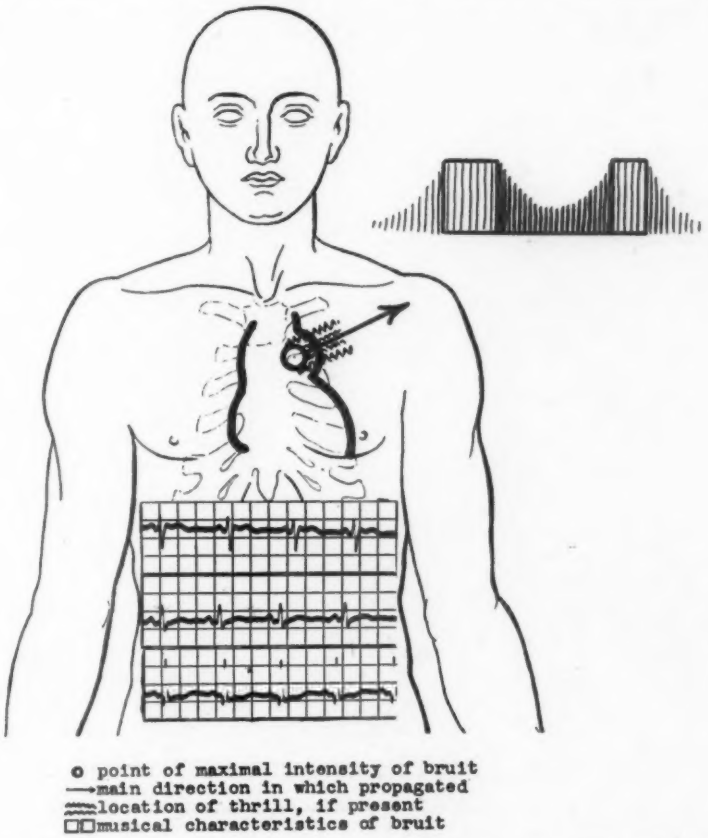


Fig. 10.—Patent ductus arteriosus (Botalli): Note the prominence of the conus shadow. The electrocardiogram shows right axis deviation.

While this is not particularly disadvantageous, it does increase the load on the right ventricle. When conditions arise which increase the pressure in the pulmonary circuit above the systemic level, a reversal of the shunt occurs, with cyanosis corresponding in degree and duration to the extent of the shunt.

The syndrome. The syndrome consists of: (1) A "machinery" or continuous murmur in the second left interspace which is transmitted toward the left shoulder, the second pulmonic sound usually being accentuated, (2) dullness in the region of the second and third left

interspaces (Gerhardt's ribbon dullness), (3) a prominent conus shadow, and (4) right axis deviation in the electrocardiogram (Fig. 10).

Comment. This is a typical example of a congenital lesion in which symptoms are absent in marked contrast to the prominent physical findings. The frequent development of subacute bacterial endocarditis renders the prognosis guarded, even though no serious mechanical difficulties are likely to develop.

*Coarctation of the Aorta.*—Mechanism. The obstruction to the aorta is usually just beyond the origin of the left subclavian artery, that

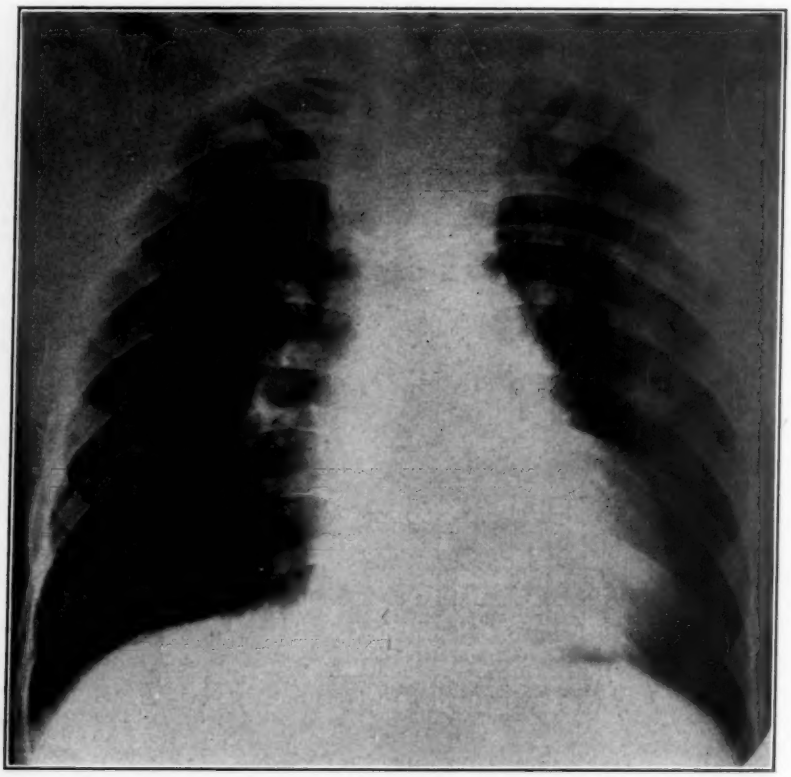

Fig. 11.—Roentgenologic appearance of coarctation of the aorta: Note the absence of the aortic knob and the erosion of many of the ribs. The left ventricle is hypertrophied.

is, at or near the junction of the ligamentum arteriosum and the aorta. The ligamentum arteriosum is the occluded ductus arteriosus, and it often remains patent when anomalies of the aortic arches are present. Interference with circulation beyond the point of obstruction depends (1) on the degree of coarctation, and (2) on the degree of collateral circulation which can be built up. The latter element, affecting mainly the intercostal arteries and the internal mammary artery and its branches, gives rise to characteristic clinical and roentgenologic findings in the form of pulsating vessels and erosion of the undersurface

of some of the ribs (Fig. 11). The obstruction also results in increased pressure in the vessels arising proximal to the point of obstruction. In these cases pulsations in the abdominal aorta and femoral vessels are markedly diminished in contrast to hypertension in the upper extremities.

The syndrome. The syndrome is as follows: (1) a systolic bruit is often present over the base and is easily confused with acquired aortic stenosis, (2) a thrill may accompany the bruit, (3) there is evidence of left ventricular hypertrophy, (4) there is electrocardiographic evidence of left ventricular strain, and (5) there is evidence of the collateral circulation just described.

Comment. Coarctation of the aorta may be latent for years, and congestive heart failure may first bring the patient to a physician. Very frequently, however, the condition terminates fatally as a result of the development of subacute bacterial endocarditis, and not a few patients die suddenly from a ruptured aneurysm of the circle of Willis, which is frequently an associated congenital anomaly. Many patients complain that their legs "go to sleep" very readily because of diminished circulation to the lower extremities. Others live to an advanced age and die from an unrelated cause.

*Persistent Right Aortic Arch.*—Mechanism: Physiologically the mechanism is perfectly normal and represents the avian arrangement. The abnormal anatomical situation, however, especially its relation to the trachea and esophagus, may cause symptoms of pressure referable to these structures.

The syndrome. The syndrome consists of (1) evidence that the ascending aorta is farther to the right than normal, namely, dullness to the right of the sternum, pulsation in the second or third right interspaces, maximal intensity of the aortic heart sounds to the right and above the usual location, and strong pulsations in the right supraclavicular fossa; and (2) characteristic roentgenologic findings, which are (a) a shadow to the right of the sternum running upward toward the right sternoclavicular joint, (b) evidence of displacement of the esophagus and trachea toward the left (this is well brought out by fluoroscopy with a barium-filled esophagus, whereas a stomach tube may be delayed at the point of displacement and transmit the pulsation from the arch of the aorta), (c) absence of the normal aortic knob in the usual situation and the presence of a retro-esophageal aortic knob determined by fluoroscopy, and (d) corroborative evidence is supplied by eliciting, fluoroscopically, a diverticulum-like structure joining the descending aorta which represents the fourth left arch beyond the point of origin of the ductus arteriosus (Fig 3).

Comment. In most of the cases described the heart is normal and symptoms may be entirely absent. So-called dysphagia lusoria resulting from esophageal displacement occurs but is frequently absent as in Arkin's cases.[1]

*Congenital Anomalies Which Are Rare But in Which the Diagnosis May Be Suspected.*—Anomalies of the coronary artery. McGinn and White[6] described the case of an infant who manifested attacks of distress on effort, such as when nursing, while the electrocardiogram showed T-wave changes of the coronary type. The heart was hypertrophied. At necropsy a single coronary artery was found arising from the pulmonary artery. The effects of anoxemia in this case were analogous to those in coronary occlusion.

Cor triloculare biatriatum. On the basis of another anomaly the same authors laid down the dictum that when in the roentgenogram a "water-bottle" shaped heart resembling a pericardial effusion is associated with intraventricular conductive disturbances in the electrocardiogram, a three-chambered heart of the foregoing type should be kept in mind.

## THE PROGNOSIS IN CONGENITAL HEART DISEASE

It is not always easy to prognosticate the future course of congenital heart disease. There is, however, with a few reservations, no reason to deviate from the usual criteria for judging cardiac efficiency. The heart is essentially a muscular pump and its main function is to maintain adequate circulation under the varying conditions incident to the daily life of the individual. With this as a premise, and it is common to all cardiac states, and with the general principle common to the wider fields of diagnostic medicine that an isolated sign rarely has much significance, the degree to which this, its main function, is interfered with in the main establishes the prognosis.

The nature and degree of the mechanical disadvantage are the first considerations; hence, again, the importance of establishing an anatomical diagnosis. In states such as patent foramen ovale, patent ductus arteriosus, maladie de Roger, and subaortic stenosis, it may be practically negligible and in spite of loud murmurs there may be little if any interference with the patient's activity. When, however, the degree of altered function is such as to place undue strain on one or more chambers of the heart, hypertrophy, dilatation, and later, loss of cardiac reserve, must inevitably follow. This undue strain is mainly brought about by abnormal shunts of blood through incomplete septa or through stenotic orifices, and finally, through extracardiac factors such as increased pressure within the pulmonary circuit. Evidence of hypertrophy or enlargement of individual chambers or of the heart as a whole then definitely influences the prognosis adversely, according to the degree of such enlargement.

The reservations previously referred to are occasioned by the vulnerability of the congenitally anomalous heart to rheumatic fever, by the frequency with which subacute bacterial endocarditis becomes engrafted upon it, and by the sudden death of an individual in appar-

ently good health. Abbott's statistical studies supply enlightening information regarding the termination in various types of congenital heart disease.[9] Small interventricular septal defects with patent ductus arteriosus may interfere very little with activity, but in from 20 to 25 per cent of cases of both types subacute bacterial endocarditis develops. In contrast, a widely patent foramen ovale is hardly ever the basis for such a complication, but in about half the cases congestive failure eventually develops. For the group of cases in which lesions involve the pulmonary infundibulum, with or without associated ventricular septal defects and the different degrees of transposition of the great vessels, the prognosis is not good. Cyanosis is likely to develop early and to be progressive, and incapacitation is the rule. Subacute bacterial endocarditis terminates life in more than 20 per cent of this group.

The individual with coarctation of the aorta leads an existence beset with even more hazards. About a third of the patients die with congestive failure; subacute bacterial endocarditis claims about 10 per cent. An unexpected and dramatic termination is not infrequently the result of subarachnoid hemorrhage due to rupture of an aneurysm of the circle of Willis, and rupture of the proximal part of the ascending aorta not infrequently occurs. Of Abbott's seventy patients with the adult type of coarctation, twenty-two died suddenly. Headaches, convulsions, and other neurological complications have been commented on.[3]

In spite of mechanical disadvantages and unpredictable hazards, however, remarkable instances of longevity have been recorded: Thus Firket's patient,[10] a woman with combined mitral stenosis and an auricular septal defect, went through eleven pregnancies and three abortions and lived to the age of seventy-four; Lutembacher's patient,[11] also a woman and with the same type of lesion, lived to be sixty-one years old and went through seven pregnancies without heart failure, and two other patients with the same types of lesions lived to the age of seventy-four and sixty-two years, respectively.[12] White and Sprague's[13] case of the tetralogy of Fallot was even more remarkable: The patient, although cyanosed, lived a full life and died at the age of fifty-nine years and eight months. Erickson and Willius[14] reported a case of widely patent foramen ovale, so wide that a normal heart could be fitted snugly into the opening; yet the patient, a man, lived to be seventy-one years old.

## SUMMARY AND CONCLUSIONS

A study of the embryology and comparative anatomy of the heart is essential in understanding the genesis and mechanism of human congenital cardiac anomalies. A number of these congenital lesions are recognizable clinically. The syndromes diagnostic or suggestive

of interventricular and interauricular septal defects, including Lutembacher's disease, subaortic and pulmonary stenosis, the tetralogy of Fallot, patent ductus arteriosus, coarctation of the aorta, persistent right aortic arch, one type of coronary artery anomaly, and the cor biatriatum triloculare have been described.

While electrocardiographic evidence is important in the recognition of congenital heart disease, there is no diagnostic picture for any type except congenital dextrocardia with complete situs transversus.

The uncomplicated septal defects, patency of the ductus arteriosus, subaortic stenosis, and persistent right aortic arch may interfere with activity only to a limited extent, but the frequent occurrence of subacute bacterial endocarditis as a complication renders their prognosis guarded. Occasionally an individual with a gross cardiac defect lives to an advanced age.

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# CHEST LEAD TRACINGS IN ARTERIAL HYPERTENSION WITH CARDIAC ENLARGEMENT

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IT IS the purpose of this presentation to call attention to a possible source of error in the interpretation of chest lead tracings in cases of arterial hypertension. In the conventional chest lead tracings,* introduced by Wolferth and Wood,[1] the ventricular complex is described as consisting of a large diphasic QRS and a large negative T-wave. Although variations in this normal pattern are not uncommon, the actual variations are usually in amplitude only. One of the limbs of the QRS, either the Q or the R may be somewhat stunted, or the T-wave may show only a shallow inversion. However, in order that the tracing shall qualify as normal, its configuration may not be altered to a point where any one of its essential features is eliminated. The initial portion of the ventricular complex should have Q and R components and the T-wave should show at least a shallow inversion.†

Classical alterations in the ventricular complex of chest lead tracings, as pointed out by Wood et al.,[2] occur generally in cases of focal myocardial damage due to an occlusion along the course of the anterior descending branch of the left coronary artery. Such alterations include: (1) Elimination of the initial component of the QRS—absence of the Q wave, and (2) positive or upwardly directed T-waves. At this stage of our familiarity with chest lead tracings it is not necessary to cite literature to prove that such changes indicate myocardial damage. The pattern is accepted as corroborative evidence in cases where the history and clinical findings suggest coronary occlusion. That the electrocardiogram is merely corroborative must be emphasized because chest lead tracings with upright T-waves, although a characteristic finding in anterior infarction, may be found in conditions other than actual cardiac infarction. Furthermore, they are not uncommonly found in apparently normal children.[3]

It is the purpose of this communication to point out that even in persons in the arteriosclerotic age group and even in those with anginal symptoms, abnormal T-waves in chest lead tracings must be evaluated with considerable caution. That is, an upright T-wave in the conventional chest lead tracing may not always be taken as an indication of a focal myocardial damage even when there are other evidences of coronary artery disease. The electrocardiographic pattern in arterial hypertension with cardiac enlargement is of special interest in this connection.

In this type of heart disease the standard electrocardiogram is often of a distinctive pattern.[4, 5, 6] It shows: (1) Moderately high voltage,

*Lead IV and/or Lead V.

†There are exceptions to this in the case of young children and, rarely, in the case of seemingly normal adults.

(2) left axis deviation, (3) inversion of $T_1$, and (4) a tall, upright $T_3$. Of course this is not, strictly speaking, a pattern of hypertension. It is the pattern rather of an enlarged and hypertrophied left ventricle which develops in a long-standing hypertension. Extreme left heart enlargement due to other causes may produce a similar pattern.

Chest lead tracings recorded from the region of the apex beat in arterial hypertension with cardiac enlargement may present a confusing picture. The reason, as indicated, is apparently anatomical.

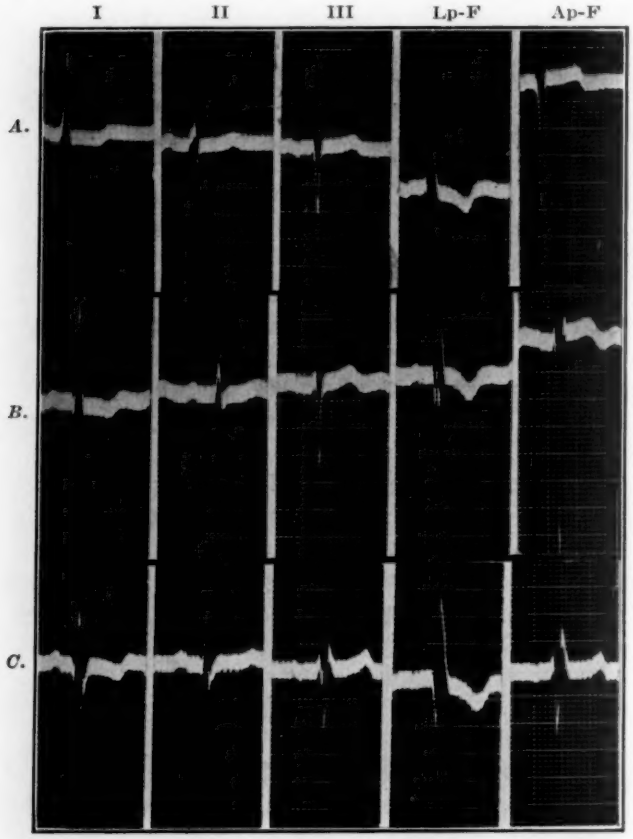


Fig. 1.—Standard Leads I, II, III, and chest leads, Left pectoral-Foot (*Lp-F*) and Apex-Foot (*Ap-F*). *A*, *B*, and *C* represent cases of arterial hypertension with cardiac enlargement. In each case $T_1$ shows inversion of its first portion, and $T_3$ is upright. The *Lp-F* chest lead shows a negative T-wave (normal pattern) and the *Ap-F* chest lead shows an upright or partly upright T-wave, resembling in general standard Lead III.

The outermost border of the left ventricle in this type of disorder often extends to or beyond the anterior axillary line. Consequently, a chest lead taken with the exploring electrode at the apex is really an axillary lead and not a pectoral lead. Axillary leads in normal persons are known to resemble standard limb leads and the axilla-foot lead of the group resembles standard Lead III. Chest lead tracings, therefore, in which the exploring electrode is situated near the axilla,

yield a record of a modified, often a magnified, standard Lead III. But, as has been pointed out above, the pattern of standard Lead III in arterial hypertension with cardiac enlargement is often characterized by a conspicuous upright T-wave. Consequently, the apical chest lead tracing, which is really an axillary tracing, also presents an upright T-wave. This may lead to confusion if we attempt to evaluate such a tracing unconditionally in the light of criteria established for normal apical chest lead tracings.

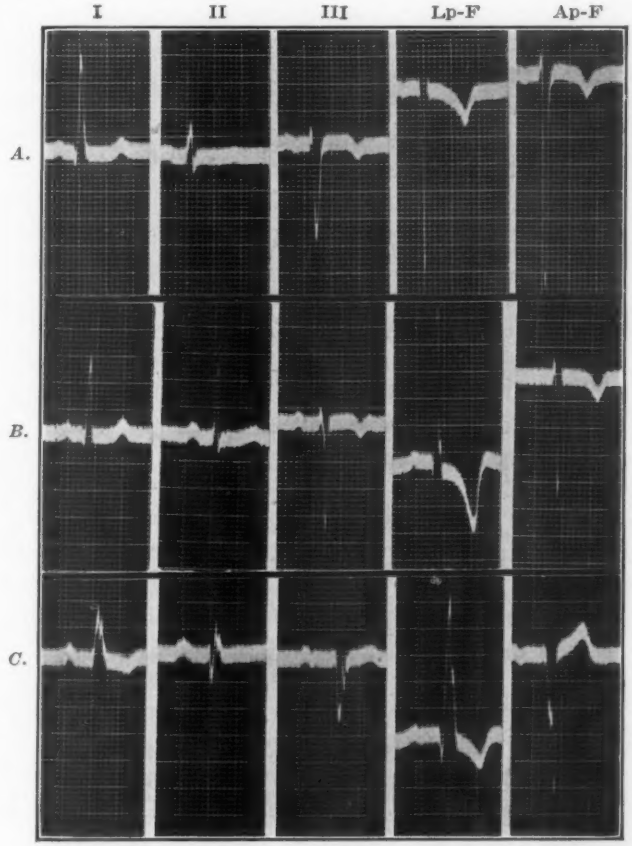


Fig. 2.—Standard Leads I, II, III, and chest leads, Left pectoral-Foot (*Lp-F*) and Apex-Foot (*Ap-F*). *A* and *B* represent cases of rheumatic aortic insufficiency with left heart enlargement. $T_3$ is negative in both. *C* represents a case of rheumatic aortic insufficiency and mitral insufficiency with a typical cor bovinum in a young man thirty-two years of age. $T_3$ is upright. Systolic blood pressure is only moderately elevated in these cases. As in Fig. 1, here too, the *Ap-F* chest lead resembles standard Lead III in each case.

Examples of such cases are presented in Fig. 1. Each case is represented by standard Leads I, II, and III, a left pectoral chest lead* and an apical chest lead. The standard leads are seen to conform to the pattern described. The left pectoral chest lead conforms to criteria established for normals. The apical chest lead, on the other hand, shows a large negative component in the QRS and a conspicu-

*Exploring electrode situated midway between the sternum and midclavicular line.

ous upright T-wave. It resembles standard Lead III. This is one of the chest lead patterns in arterial hypertension with cardiac enlargement.

In order to show that the abnormal T-wave is probably due to the axillary application of the exploring electrode necessitated by the displacement of the apex impulse as a result of cardiac enlargement, cases with left heart enlargement due to causes other than arterial hypertension were chosen for comparison. These are presented in Fig. 2. Graphs *A* and *B* each represent a case of rheumatic aortic insufficiency with only a moderate systolic hypertension, not above 160 mm. in either case. In these the T-waves in Lead III of the standard electrocardiogram are negative. Graph *C* represents a case of rheumatic aortic and mitral insufficiency with systolic pressure well within the upper limit of normal. In this case, standard Lead III shows an upright T-wave. Because of marked displacement of the left border of the heart, the apex chest lead in this group had to be taken with the exploring electrode situated at or near the anterior axillary line. As seen in the figure, the ventricular complexes of the apex chest lead tracings resemble those of standard Lead III in each case. In graphs *A* and *B*, the ventricular complex shows an inverted T-wave while in graph *C* the T-wave is upright.

In clinical electrocardiography, especially in the busy laboratory, where daily reporting of tracings is a pressing task, there is a tendency to lean on cardiographic patterns as a matter of convenience in routine reporting. Criteria for diagnosis are eagerly sought and are often employed without a knowledge of the clinical history or physical findings in the case. Electrocardiographic "evidences of myocardial damage" are often reported on findings less convincing than T-wave changes in chest lead tracings. Consequently, upright T-waves such as are seen in the apex chest lead in certain cases of arterial hypertension with cardiac enlargement may naturally prompt a diagnosis of myocardial infarction. It is realized that cases of hypertensive heart disease often have sclerosis of the coronary arteries and, at times, even myocardial infarction, but it must be emphasized that the upright T-wave seen in the apex chest lead in such cases *may not* be taken as the criterion upon which to base the diagnosis.

In a previous publication[7] it has been pointed out that in selecting the site of application of the exploring electrode in chest leads, the apex, because of its elusiveness, is perhaps the least reliable site. In persons of middle age it is at times difficult to locate the apex beat with any degree of accuracy. We may now add that the so-called apex lead in cases of arterial hypertension at times yields a tracing of an actually deceptive pattern in that it includes an upright, abnormal T-wave which may lead to a faulty diagnosis.

On the other hand, as the tracings in Figs. 1 and 2 show in cases of arterial hypertension with cardiac enlargement, even of a degree sufficient to produce a distinctive pattern in the standard leads, the

left pectoral chest lead tracing is not appreciably altered. This is of considerable importance. It is well known that in coronary occlusion of the anterior type, it is precisely this lead which shows the most marked T-wave changes. Consequently, the left pectoral chest lead may be used for the purpose of a differential diagnosis in cases of left heart enlargement when a myocardial infarction is suspected. Furthermore, as has been said, the electrocardiographic pattern of the apical chest lead in hypertensive heart disease is characterized by a QRS which has a large negative component. In cardiac infarction, on the other hand, due to thrombosis along the course of the anterior left descending coronary artery, the left pectoral chest lead tracing is generally characterized by a complete absence of the negative component. The contrast between the patterns of the left pectoral and apex chest leads in arterial hypertension with cardiac enlargement is conspicuous.

SUMMARY

An electrocardiographic pattern of the apical chest lead tracing in certain cases of arterial hypertension with cardiac enlargement has been presented. The ventricular complex in this tracing is characterized by a QRS which consists predominantly of a large negative component and by an upright T-wave. The pattern is essentially a modified standard Lead III, and is due, apparently, to the axillary situation of the exploring electrode.

Examples of left heart enlargement in cases of rheumatic aortic insufficiency, some having negative, others positive, T-waves in standard Lead III, are presented for comparison to show that in these cases too, the apical chest lead tracing resembles standard Lead III.

The left pectoral chest lead tracing is not appreciably altered in these cases, and, therefore, stands out in marked contrast with the apical lead. This lead, therefore, may serve in problems of differential diagnosis. In fact, the left pectoral lead is the chest lead of choice and the so-called apical lead should be avoided as a routine lead in cases of arterial hypertension with left heart enlargement.

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# CORONARY AND EXTRACORONARY FACTORS IN HYPERTENSIVE HEART FAILURE*

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CONGESTIVE heart failure is a common sequel of long-standing hypertension. Various physiological and pathological factors, such as coronary sclerosis, myofibrosis cordis, strain and fatigue, have been assigned rôles in heart failure of this type. The evidence that there is no histological equivalent for cardiac insufficiency or failure has been epitomized by Aschoff and Tawara.[1] More recently, since anatomical and physiological considerations have left the question open, attention has been paid to the rôle of metabolic disturbances in the causation of the failure of the hypertensive heart. In this study, the factors concerned in the failure of hypertensive hearts free of significant coronary disease have been considered. As a control group, a series of 40 hypertensive cases with chronic congestive heart failure and varying degrees of coronary artery disease have also been analyzed.

## MATERIALS

Congestive heart failure was considered to have been present when there was a history or signs of paroxysmal dyspnea or pulmonary edema, or when there was fluid retention manifested by hepatic or pulmonary congestion and latent or visible edema. The material comprised 21 cases of hypertension with congestive heart failure and minimal coronary disease and no gross myocardial damage, 40 with congestive heart failure and varying degrees of coronary disease, 8 hypertensive cases with coronary disease and no congestive heart failure, and 8 normal hearts. Numerous cross-sections of the hearts were made along the longitudinal courses of the coronary arteries. Blocks of tissue were taken from those areas which are frequently the sites of cardiac infarction, namely: (1) the junction of the upper and middle thirds of the interventricular septum, (2) the interventricular septum at the apex, (3) the apical region of the right ventricle, (4) the apical region of the left ventricle, (5) the posterior mitral region, and (6) the anterior papillary muscle of the left ventricle in some cases.

Paraffin sections were stained with hematoxylin-eosin and Verhoeff-van Gieson's mixture. Particular attention was paid to muscle fiber hypertrophy, to the presence or absence of increased or dilated sinusoids and to myocardial fibrosis. Attention was also paid to the relationship of vascular lesions to myocardial fibrosis. Since separation of the branches of the coronary arterial tree by muscle hyper-

*From the Medical and Laboratory Divisions, Montefiore Hospital.

trophy may play a rôle in congestive heart failure by producing anoxemia, the number of arterioles per unit area of heart tissue was counted. A summary of these counts is reproduced in Table I.

## FINDINGS

*Pathological.*—The coronary arteries of persons in the fourth decade commonly show changes when these individuals have had neither history nor signs of arteriosclerotic heart disease. Since we are dealing with cases at or beyond middle life and furthermore since hypertension hastens the tempo of development of arteriosclerosis, there was in no case complete absence of degenerative coronary artery disease. In that sense, there is no hypertension without coronary arteriosclerosis.

TABLE I

ARTERIOLE COUNTS

| HEART WEIGHT IN GRAMS | NUMBER OF CASES | AVERAGE NUMBER OF ARTERIOLES PER LOW POWER FIELD (AVERAGE OF 10 FIELDS) |
|---|---|---|
| 200 to 300 | 9 | 3.14 |
| 300 to 400 | 5 | 2.20 |
| 400 to 500 | 4 | 1.42 |
| 500 to 900 | 10 | 1.13 |

*Histology of Myocardial Hypertrophy.*—Cardiac hypertrophy, macroscopic and microscopic, is the finding common to practically all cases of chronic congestive heart failure. This hypertrophy is due, according to Karsner, Saphir, and Todd,[2] solely to an increase in size of the individual fibers, since there is no actual increase in their number. The enormous size attained by some of the hypertrophied fibers may be seen by direct comparison with the normal fiber under the camera lucida, Fig. 1. The myofibrillae themselves are thicker than normal. The outline of the hypertrophied muscle fiber is frequently irregular, due to infoldings of the surface. The normal shallow grooves or slits may become so deepened that the enlarged fiber appears scalloped in cross-section. It is possible that this surface irregularity of the hypertrophied muscle fiber serves the physiological purpose of increasing the surface for greater diffusion of oxygen and metabolites. The presence of blood capillaries in the bottom of these grooves, Fig. 1 *C*, would favor the view that this is an additional adaptive mechanism.

The nuclei of the hypertrophied muscle fibers show profound changes. The nucleus of the normal muscle fiber shows some degree of surface irregularity and both binucleated and multinucleated forms occasionally occur. The changes in the early phases of cardiac hypertrophy are slight increases in the size of nuclei, squaring of their ends, and irregularities of contour. The nuclear changes in the hypertrophied fiber are merely an accentuation of the normal irregularity.

They were observed as far back as 1889 by Tangl,[3] though there has been no agreement as to their significance. As the nuclei increase in size progressively, they assume bizarre shapes, becoming elongated, square, C-shaped, or even totally irregular. On cross-section, this change is even more evident. All gradations from slight surface wrinkling to extensive stellate branching are seen. There is a rough

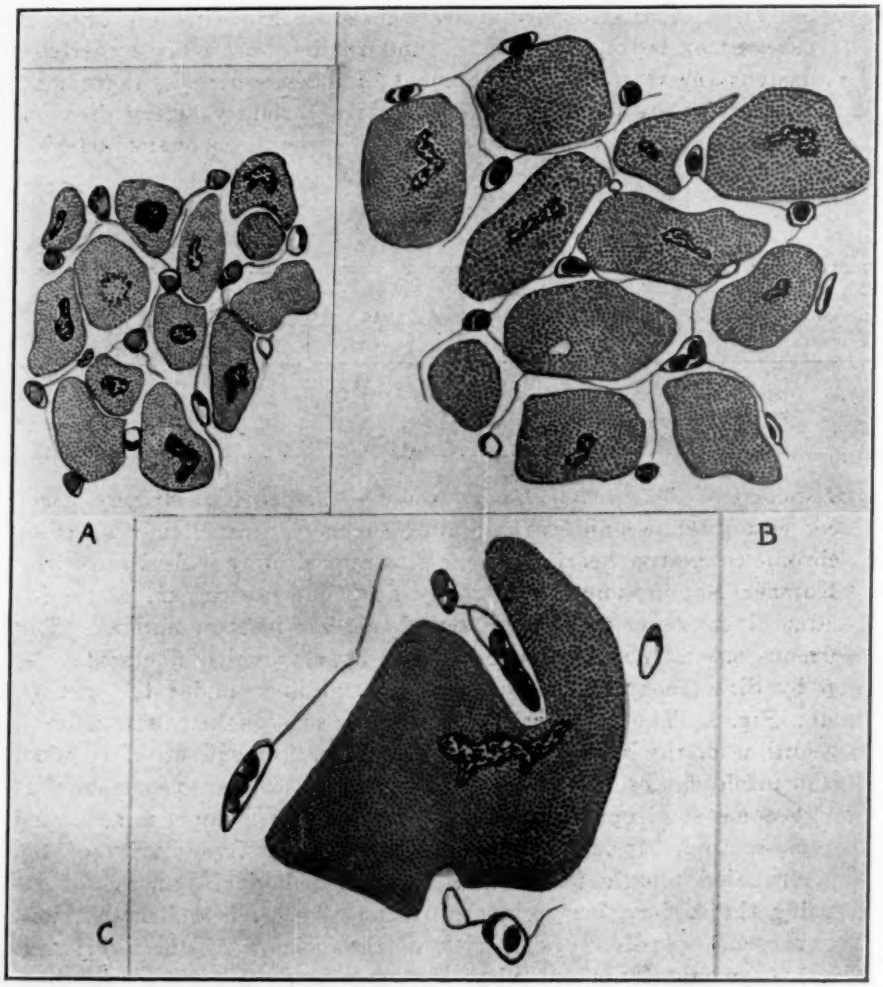


**Fig. 1.—Camera lucida drawings of cross-sections of muscle fibers from the left ventricle, reproduced on the same scale. Magnification of approximately 400 diameters.**

***A.*—Normal heart. Weight 300 gm.**
***B.*—Hypertrophied heart. Weight 600 gm.**
***C.*—Hypertrophied heart. Weight 750 gm.**

**Note the relationship between the capillary bed and the cross-sectional area of myocardium. The huge muscle fiber in Fig. 3 is not unusual in marked cardiac hypertrophy.**

direct relationship between fiber size and nuclear irregularity, the largest fibers having the most bizarre nuclei. It seems to us that

these nuclear alterations represent an attempt to increase the surface area of the nucleus in order to provide for a better interchange of metabolites.

The chromatin content of the hypertrophied nucleus is usually increased, though at times it is diminished. Cohn[4] has observed a decrease in chromatin in cardiac hypertrophy.

Enlargement of the muscle fibers results also in a change in the nucleosarcoplasmic ratio. Collier[5] noted no change in nucleosarcoplasmic ratio in slight cardiac hypertrophy in dogs and rats. Preliminary quantitative measurements of this ratio in our material showed alterations due to a preponderance in volume of sarcoplasm in marked hypertrophy, and inconstant variations in the ratio in slight to moderate cardiac hypertrophy.

A striking feature of the histological picture of the hypertrophied myocardium is the paucity of arterioles and small arteries per unit area of heart muscle. Counts were made in 28 cases. In normal and enlarged hearts, counts of these vessels showed that there was roughly an inverse relationship between the size of the heart and the number of arterioles and small arteries per unit area.

Capillary counts were made by Wearn[6] who found an average of one capillary per muscle fiber in the normal heart. However, in the hypertrophied heart, the average per unit area is much less. The relationship between capillary bed and volume of myocardium supplied is graphically illustrated in Fig. 1. This fact, noted by us in hypertrophied human hearts, was recently confirmed experimentally by Shipley et al.[7]

There was no constant relationship between coronary arteriosclerosis and myocardial fibrosis. Every case of cardiac hypertrophy showed some increase of connective tissue, even though it may have been extremely slight. This increase in connective tissue was not directly dependent on coronary arteriosclerosis. In a control group of 8 hearts from patients of middle and advanced ages, there was an absence of even microscopic scarring in most instances. In almost all cases of cardiac hypertrophy, in which no scarring was evident microscopically, some degree of myofibrosis was seen on microscopic examination. Frequently, the area of scarring was of the width of only several muscle fibers, and in a few instances, the areas were almost macroscopic. Varying proportions of elastic tissue were present in the scars.

At least three types of histological changes were observed in the development of myocardial fibrosis. These were: (1) microscopic areas of coagulation necrosis, constituting miniature acute infarcts, similar in all respects to gross cardiac infarction following major coronary occlusion. All stages of replacement fibrosis were noted. This change was preceded by an ingrowth of granulation tissue which

finally became poor in fibroblasts and capillaries. (2) A slower process of fiber dissolution, namely, fatty degeneration terminating in cell death. In areas of varying microscopic size, all gradations were noted from accumulation of vacuoles within the muscle fibers to replacement by granulation tissue. Nuclear pyknosis and fragmentation accompanied the advanced stages of fatty degeneration. In the terminal phase, the muscle fiber consisted of a cell membrane, fat vacuoles and a fragmented pyknotic nucleus. Cell death was followed by invasion of macrophages, capillaries, and fibroblasts. The end stage of this process in the myocardium was replacement fibrosis. (3) The third type of change was seen in the very large hearts and consisted of a loss of myofibrillae with an insensible merging of connective tissue and muscle fibers. The resulting scars were as small as the width of single muscle fibers.

The perivascular connective tissue was increased in most instances of cardiac hypertrophy. This alteration was independent of myocardial fibrosis and represented a thickening of the connective tissue framework of the heart.

We observed an abundance of sinusoids in many instances of cardiac hypertrophy both with and without coronary artery disease. These were more conspicuous in the hypertrophied than in the normal heart. They arise by a widening of pre-existing channels and consist of a single layer of endothelium. A gradual transition may be seen between the sinusoids and the veins entering the epicardium. The sinusoids are numerous at the apical portion of the interventricular septum and the lower half of the left ventricle and are most numerous in the inner half of the myocardium where they empty into the pockets of the trabeculae carneae. Hearts weighing from 400 to 500 gm. had a slight increase of sinusoids, while those weighing more than 500 gm. frequently had a marked increase of sinusoids. Only a few red blood cells are seen in the lumens of these vessels and in but a few instances have we observed them to be engorged with blood.

Inconstant medial hypertrophy was noted in the smaller arteries and arterioles. This appears to be a compensatory mechanism in hypertensive hearts. The myocardial branches rarely showed changes other than slight reduplication of the internal elastic lamella, which, in addition, often showed splitting and irregularity.

## SUMMARY OF CLINICOPATHOLOGICAL FINDINGS

Twenty-one patients had, grossly, minimal coronary artery disease. Of these, 13 had minimal coronary artery disease, both macroscopically and microscopically. Four were males and 9 were females. The heart weights varied between 420 and 880 gm., the average weight being 661 gm. In only 6 of the 13 was congestive heart failure less than two years in duration. In the majority, the failure lasted up to ten years. No correlation, however, could be made between heart weight

and duration or severity of failure. Evidently, some factor besides heart weight determines the onset of congestive heart failure.

In the remaining 8 patients, the coronary arteries were soft and grossly showed minimal arteriosclerosis, but microscopically, there were stenosing plaques of varying size. These cases comprised 5 males and 3 females. The heart weights varied between 520 and 1,050 gm., the average being 672 gm. Despite greater coronary disease, there

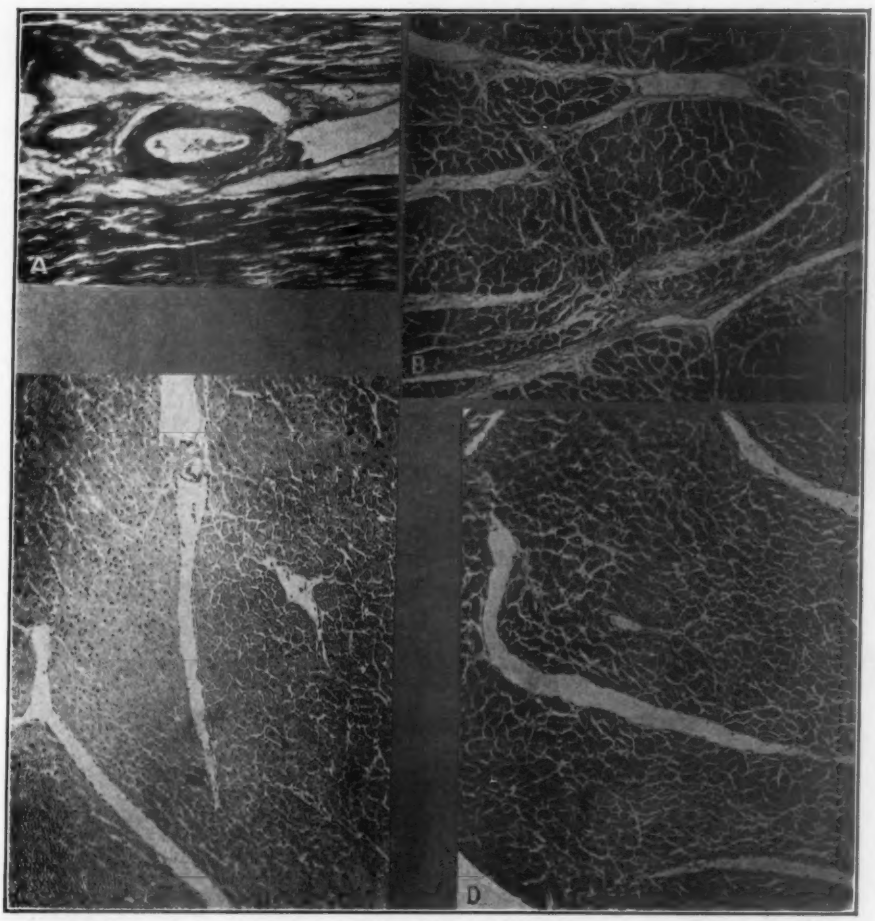


Fig. 2.—All sections from the left ventricle.
*A.*—Heart weight 880 gm. ×60. Shows thickening of the medial coat in a medium sized myocardial artery.
*B.*—Heart weight 540 gm. ×240. Marked coronary arteriosclerosis with occlusion of left circumflex artery. Several sinusoids are shown.
*C.*—Heart weight 380 gm. ×240. Slight coronary arteriosclerosis. Several branching sinusoids may be noted.
*D.*—Heart weight 600 gm. ×240. Minimal coronary arteriosclerosis. Four parallel sinusoids are shown.

was no relationship, however, between the severity and duration of heart failure and heart weight. It is noteworthy in this group, despite slightly greater coronary atherosclerosis, that congestive heart failure lasted longer than in the group with minimal coronary disease.

The causes of death in the first group of 13 were cerebral accidents in five and cardiac failure in three. The remainder had uremia or bronchopneumonia, and one died of a surgical complication. The causes of death in the eight cases with partially occluding plaques in the coronary arteries were congestive heart failure in two, sudden death in one, and bronchopneumonia or surgical complications in the remainder.

As a control group, 40 patients with congestive heart failure and varying degrees of coronary arteriosclerosis or thrombosis and myocardial infarction were studied. Divided according to sex, there were

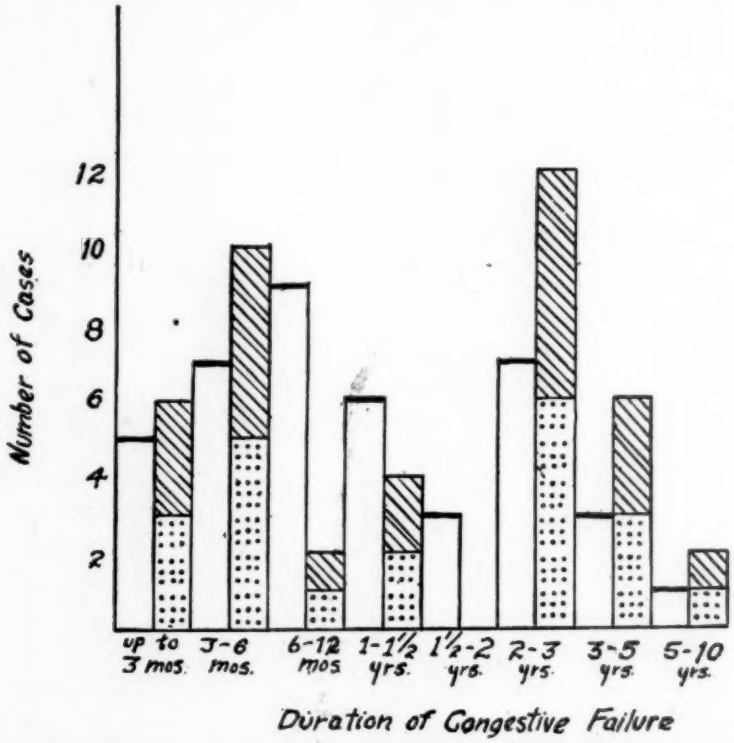


Fig. 3.—Showing duration of congestive heart failure in cases with and without major coronary arteriosclerosis. Table corrected for comparison of equal number of cases. Open spaces indicate number of cases of major coronary disease. Dotted boxes indicate number of cases of minimal coronary disease. Cross-hatched boxes indicate corrected number of cases of minimal coronary arteriosclerosis.

21 males and 19 females. Though hypertension is more common in women, the combination of hypertensive arteriosclerotic heart disease is usually severer and runs a shorter course in males. This was also the case in our material.

Cardiac hypertrophy was present in all but one case and is to be attributed to essential hypertension, since coronary disease alone does not cause cardiac hypertrophy. Of five cases of failure in hearts weighing less than 400 gm., failure was late in onset and was mild

in all. Two of these patients died in uremia which may have been a determining cause of water retention. The causes of death of the entire group are tabulated in Table II.

TABLE II

CAUSES OF DEATH IN 40 CASES OF CONGESTIVE HEART FAILURE ASSOCIATED WITH SEVERE CORONARY DISEASE

| | |
|---|---|
| Bronchopneumonia | 10 |
| Congestive heart failure (of these, one had bronchopneumonia and another, terminal uremia) | 8 |
| Uremia | 6 |
| Cerebral | 5 |
| Sudden unexplained | 5 |
| Convulsions | 2 |
| Postoperative cardiac failure | 1 |
| Following an anginal seizure | 1 |
| Following an acute coronary thrombosis | 1 |
| Pulmonary edema | 1 |
| Total | 40 |

In another control group of 8 patients with essential hypertension with moderate and, in some cases, severe coronary artery disease and varying degrees of myocardial damage, congestive heart failure did not occur. The heart weights in all but two were 400 gm. or less. The heart weights of these two were 500 and 550 gm. In this group, there was also no correlation between myocardial scarring and vessel damage. The average heart weight of the cases of severe coronary disease with congestive heart failure was 554 gm., and is definitely lower than the average heart weight of cases with minimal coronary artery disease. Evidently, in the presence of coronary arteriosclerosis, the hypertensive cardiac patient dies from congestive heart failure and other causes often before the heart becomes massive.

Progressive or sudden additional coronary narrowing is associated with an impairment of nutrition responsible for more or less acute congestive heart failure in many cases of cardiac hypertrophy and occurred six times. Reference to Fig. 3 shows strikingly that in patients with severe coronary disease, the duration of failure was distinctly shorter than in those with minimal coronary sclerosis. In only 27.5 per cent of the cases with severe coronary disease was the duration of failure over two years. It is noteworthy that of all the hearts in failure weighing 500 gm. or more, 61 per cent had minimal coronary artery disease, Fig. 4. In both groups of cases, however, there was no correlation in any individual case between heart weight and duration of failure, nor was there a relation between muscle and vessel damage and failure. These facts point to the rôle of extracoronary vascular factors in hypertensive heart failure.

TABLE III

RELATION OF DURATION OF CONGESTIVE HEART FAILURE TO HEART WEIGHT IN THE PATIENTS WITH MAJOR AND MINIMAL CORONARY ARTERY DISEASE

| | LESS THAN 400 GM. | | 400 TO 500 GM. | | 500 TO 600 GM. | | 600 TO 700 GM. | | 700 TO 800 GM. | | 800 TO 900 GM. | | OVER 900 GM. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCD* | MCD | SCD | MCD | SCD | MCD | SCD | MCD | SCD | MCD | SCD | MCD | SCD | MCD |
| Up to 3 mo. | | | 1 | 1 | 2 | 1 | 1 | | | | | 1 | 1 | |
| 3 to 6 mo. | | | 4 | 1 | 1 | 1 | | 2 | | | | 1 | | |
| 6 to 12 mo. | 3 | | 2 | | 2 | | 2 | | 1 | | | | | 1 |
| 1 to 1½ yr. | 1 | | 2 | | 2 | 1 | 1 | 1 | | | | | | |
| 1½ to 2 yr. | | | 1 | | 2 | | | | | | | | | |
| 2 to 3 yr. | | | 1 | | 1 | 3 | 4 | 1 | | | 1 | 2 | | |
| 3 to 5 yr. | | | 1 | | 2 | 2 | | | | 1 | | | | |
| 5 to 10 yr. | | | | | | | | 1 | 1 | | | | | |

*SCD—Severe coronary disease.
MCD—Minimal coronary disease.

## DISCUSSION

The prime purpose of this study was a survey of hypertensive heart failure in cases in which coronary arteriosclerosis was insignificant. The material with severe coronary disease served merely as controls. Nevertheless, no study of chronic congestive failure occurring in hypertension is complete without adequate consideration of the rôle of the coronary arteries.

Leyden[8] was among the first of modern clinicians to give a comprehensive description of the clinical and pathological aspects of acute and chronic coronary artery disease. Lisa[9] found that with the excep-

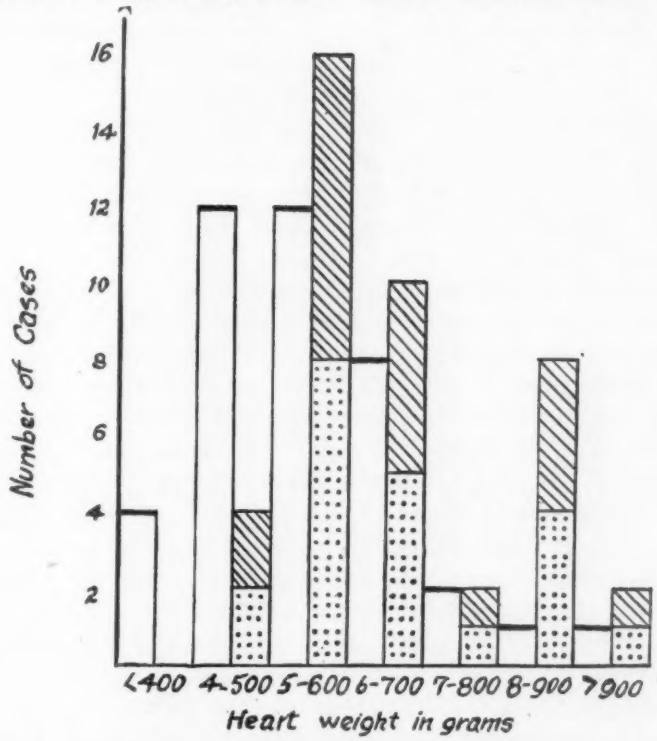


Fig. 4.—Showing tabulation of cases of major and minimal coronary arteriosclerosis against heart weight. This table indicates that the cases with minimal coronary arteriosclerosis had greater heart weights. Of the hearts of both groups weighing 500 gm. or more, 61 per cent had minimal coronary artery disease.

tion of very small scars, chiefly in the left ventricle and interventricular septum, the myocardium presented no marked gross changes in cases of hypertension without major coronary artery disease. Bell and Clawson,[10] in a study of 420 cases of essential hypertension, noted myocardial insufficiency in 187 instances and symptoms referable primarily to the coronary arteries in a group of 67 patients. Coronary sclerosis was more common and more severe in the hypertensive cases than in those of nonhypertensive heart disease. It is striking that in the hearts weighing 400 gm. or less, myocardial insufficiency was un-

common, while in those weighing 500 gm. or more, myocardial insufficiency was frequent. The average heart weight of those showing myocardial insufficiency was highest in their entire series and decidedly higher than in the group with coronary disease as the salient condition.

Clawson[11] studied 139 cases of hypertension in a survey of 429 cases of cardiac failure. Of these 139 patients the causes of death were: in 78, cardiac failure; in 37, coronary sclerosis; in 16, cerebral arteriosclerosis; and in 8, renal insufficiency. Among the 78 that died from congestive heart failure, there was no cellular proliferation or exudation in the myocardium except in those with infarcts. Severe coronary sclerosis was present in 15.5 per cent and severe myocardial fibrosis in only 2.5 per cent. Slight coronary sclerosis was present in 69 per cent and slight myocardial fibrosis was noted in 44.5 per cent. There was no narrowing of the coronary arteries in 15.5 per cent and no myocardial fibrosis in 52.5 per cent of the cases. Clawson was of the belief that myocardial fibrosis is of little importance in bringing about myocardial failure in hypertension, since myocardial fibrosis is common to patients with and without hypertension.

Christian,[12] in discussing the problem of hypertensive heart disease, also noted that the hypertrophy of the heart was the striking feature of the cases in failure, whereas many patients with symptomless hypertension had little or no cardiac hypertrophy. He raised the question of the rôle of anoxemia in congestive heart failure, for he believed that in cardiac hypertrophy the capillaries do not increase in number. Furthermore, when the capillaries become widely separated, there is a diminished supply of nutritive materials and oxygen and improper removal of metabolites. This conjecture was observed by us to be true.

Arteriolar counts in our material revealed an inverse relationship between the number of arterioles and heart weight. It is apparent that with an increase in width of the muscle fibers, the vessels would be called upon to supply an increased volume of myocardium in proportion to the degree of hypertrophy. The demand would be even greater in the presence of major coronary artery disease. This separation may also produce stretching of the vessel walls and a decrease in tortuosity which may be related to the dynamics of blood flow.

Averbuck,[13] after studying 40 cases, concluded that heart failure in hypertension was most commonly due to coronary sclerosis and thrombosis. Nemet and Gross,[14] however, in studying 100 cases of arteriosclerotic heart disease, found coronary vessel and muscle damage as common in patients without congestive heart failure as in those with congestive failure.

Nathanson,[15] in a series of 113 cases of coronary artery disease, observed congestive heart failure in but 6.6 per cent of those with normal sized hearts, while in the group with cardiac enlargement, congestive heart failure occurred in 63.2 per cent. It is striking that of the group in congestive heart failure, cardiac enlargement was

present in 93.4 per cent. It is evident that the distinguishing feature of our cases in failure as well as of those recorded in the literature is the presence of cardiac hypertrophy in those in failure and its infrequence in those not in failure.

Wiggers[16] stated that the volume of flow through coronary artery collateral vessels depends upon the magnitude of pressure differences. In slow occlusion, altered pressure gradients distend normally useless channels. At such times, the pressure gradients are favorable for the development of flow through coronary and extracoronary anastomoses. A flow from the ventricular cavity to the artery during systolic ejection may develop and a to-and-fro movement could occur during each heart cycle.

Since death in coronary disease does not usually occur after the first attack, both intracardiac and extracardiac collaterals may subsequently arise so that the circulation is actually improved. So far as the circulation itself is concerned, some factor besides coronary disease must be the cause of congestive heart failure, since, in the surviving heart, the blood supply is greater than at the time of thrombosis.

The rôle of myocardial fibrosis in cardiac hypertrophy has occupied the attention of many pathologists. Moenckeberg[17] quoted Goldenberg[18] who observed regularly in cardiac hypertrophy a spreading out of the connective tissue septa between the individual muscle fibers. This replacement fibrosis was found to be a variable process, and was greater in some areas than in others. Tangl[3] denied that cardiac hypertrophy was associated with myocardial fibrosis. Dehio,[19] however, observed in hypertrophied hearts, a diffuse increase in connective tissue which he called myofibrosis cordis. The fibrosis was in proportion to the extent and duration of the hypertrophy and failure. The degree of fibrosis was proportional to the dilatation of the heart chambers. It is, furthermore, noteworthy that Bell and Clawson,[10] Levine,[20] Lisa,[9] V. Levine,[21] and Plaut and Kramer[22] observed no correlation between vascular and muscular lesions.

Saphir[23] et al cited cases of myocardial infarcts without complete coronary obstruction and attributed infarction to temporary coronary insufficiency resulting in lowered arterial pressure so that the infarcted area temporarily is inadequately supplied with blood. Plaut and Kramer[22] mentioned anemia, collateral circulation, and other factors bearing on this relationship and reported a case of myocardial infarction associated solely with arteriolosclerosis. Dehio[19] felt then, as there is good reason to believe now, that a contributory cause to myofibrosis cordis is increased intracardiac diastolic blood pressure, due to cardiac dilatation, leading to capillary stasis and induration. In this manner, on purely dynamic grounds, it is possible to explain both patchy myocardial fibrosis and the independence of myocardial fibrosis from coronary disease. The small areas of fibrosis in the myocardium of hypertensive hearts appear to us to be concomitant with

or a by-product of the hypertrophied heart rather than a cause of heart failure. The danger of drawing too close a cause-and-effect relationship, even in the presence of coronary arteriosclerosis, is apparent.

It is well established that vascular spasm may play a significant rôle in clinical medicine. Ricker[24] observed that vascular segments form autonomous units with the vascular response dependent upon the strength of the stimulus. According to him, spasm may be followed by stasis and paralysis of a vascular segment. F. Lange[25] noted that weak stimuli produce vasodilatation and strong stimuli cause vasoconstriction. With very strong stimuli, constriction is followed by paralysis of the vessel wall. Vascular necrosis may follow dilatation and slowing of the circulation that has lasted for a long time. Lewis and Landis,[26] using ergot, made similar observations and produced necrosis of the cock's comb from circulatory stasis. In the stages of stasis or thrombosis, local arrest of the circulation and gangrene of the comb developed. The implications of the concept of arterial spasm for clinical medicine are far reaching and important in explaining the disparity between morbid physiology and morbid anatomy.

If the concept of vascular spasm is accepted, it is conceivable that an area of tissue supplied by a spastic vessel may undergo necrobiosis of varying degrees depending upon the severity and duration of the vascular reaction. This theory would explain the frequency of myocardial fibrosis observed by Neubuerger[27] in epileptics in the absence of corresponding vascular damage. Likewise, vascular spasm is compatible with the occurrence of sudden anginal seizures and the well-known cases of sudden death, in the absence of anatomical cause of death.

V. Levine[21] attributed significance to the rôle of vascular spasm since he could not find an organic basis for myocardial scarring in many of his cases of hypertensive heart failure. Jaffé and Bross[28] cite a case of sudden death, found at necropsy to have delicate coronary arteries and on histological examination, an acute myocardial exudate. They believed death was due to a functional vascular disturbance.

It is the experience of many pathologists that there is a lack of exact correlation between major coronary vessel disease and muscle damage. This disparity may be explained by mechanical or functional considerations. Cases have been recorded, and we have observed instances, of single or of even double coronary artery thrombosis without myocardial infarction. Furthermore, myocardial infarction without a corresponding coronary artery occlusion has also been reported. Some extracoronary, or even extracardiac factor or factors must play a rôle in the nutrition of the heart. Perhaps these factors also play a part in the aging of the heart and in providing nutrition to counteract advancing coronary arteriosclerosis.

Moritz, Hudson, and Orgain[29] established the existence of extracardiac anastomoses through pericardial adhesions. Beck and Tichy[30] observed that coronary thrombosis was better tolerated if a previous collateral circulation had been prepared. Wearn[31, 32] and his coworkers reported the existence of communications, the thebesian vessels, between the coronary arteries and veins and the chambers of the heart and that as much as 90 per cent of the arterial blood may escape through the thebesian vessels. Leary and Wearn[33] reached this conclusion from cases of occlusions of both coronary arteries without associated myocardial damage.

Kretz[34] was of the belief that the thebesian vessels account for the disproportion between morbid changes of the coronary arteries and cardiac function. He thought that despite marked coronary damage the heart may be fully capable of performing its work. In a case of tuberculous myocarditis with destruction of the large coronary arteries and veins, Bellet, Gouley, and McMillan[35] found the thebesian vessels dilated and connecting the myocardium with the remaining intramural veins. Bohning, Jochim, and Katz[36] believed the thebesian vessels may nourish the heart in pathological conditions. The rôle of the thebesian vessels, however, was denied by Robertson[37] who thought that vascular pericardial adhesions play a rôle in the nourishment of the heart. Batson and Bellet[38] were of the belief that reversal of flow in the coronary veins is another factor in the nourishment of the heart. The efficacy of this pathway was recently denied by Wiggers.[16]

In our material, an increase of sinusoids was observed in cardiac hypertrophy in some cases. In small hearts, despite coronary disease, however, they were either not increased or when increased, this increase was never more than minimal. Numerical analysis of the sinusoids reveals no exact correlation with either duration or severity of congestive heart failure, cardiac hypertrophy, or coronary disease. This is as is to be expected since an increase in sinusoids is but one of several possible mechanisms by which the circulation to the heart itself is maintained. The striking feature is, however, the noteworthy frequency with which this mechanism is brought into play in enlarged hearts.

The existence of these additional vascular channels accounts for the lack of correspondence between vascular and myocardial damage. These pathways may explain, further, why, with similar muscle and vessel damage, some hearts go into congestive heart failure sooner than others and why enormous hearts even with severe coronary disease resist congestive heart failure a long time. It is thus easily understandable why the anatomical examination of a heart yields no insight into its physiological activity during life.

*Cardiac Hypertrophy.*—It is a generally accepted physiological maxim that when a muscle is required to do increased work, it undergoes hypertrophy. As a corollary, it may be said that if a muscle is found

to be hypertrophied, the conclusion is justifiable that it has performed increased work. The human heart, by increase of its muscle mass, is also capable of doing more work. While the condition responsible for such increase in mass is a disease, muscle hypertrophy is merely a mechanical response to compensate for increased diastolic stretching. Cardiac hypertrophy similarly, in itself, is not a disease. In fact, the hypertrophied muscle is stronger than the ordinary to meet increased physiological demands. Failure of the mechanism responsible for cardiac hypertrophy, however, results in a decrease of contractile power. At such times, hypertrophy no longer occurs, despite the persistence of the cause responsible for hypertrophy.

Dilatation of the heart muscle, as in any other muscle, is in itself also not a sinister process. In fact, temporarily increased demands on the normal heart can only be met by increase in diastolic fiber length or fiber tension which is the physiological response to demand for increased work. Furthermore, without such increase in diastolic fiber length, its counterpart, cardiac hypertrophy, does not appear. When, however, for some unknown reason, dilatation ceases to produce the stimulus for hypertrophy and dilatation is progressive, the pernicious effects of dilatation alone are in evidence. At such times, increased fiber length is not associated with an increase in the height of the isometric muscle contraction curve. It follows, therefore, that dilatation, which is the means by which the heart hypertrophies and does more work, is also the mechanism by which cardiac insufficiency ultimately develops.

Cardiac enlargement is a cardinal feature in chronic congestive heart failure of all types, and is not limited to the hypertensive heart. Christian[12] has suggested that the mechanism of cardiac hypertrophy and failure may be the same in patients with and without valvular disease. In rheumatic heart disease, congestive heart failure is very frequently associated with active carditis, as shown by Rothschild, Kugel, and Gross.[39] However, in the cases not showing active carditis, we have noted the frequent incidence of marked cardiac hypertrophy. The insufficiency of the pulmonic circulation also has been shown by Fineberg and Wiggers[40] to be dependent upon fatigue of the right ventricle.

In syphilitic aortic insufficiency, too, congestive heart failure occurs practically always in massive hearts. Clawson and Bell[41] felt that in syphilitic heart disease, the most conspicuous change in the myocardium was hypertrophy, and that little attention need be paid to the gross or microscopic changes. In these cases congestive heart failure is not related to the state of the coronary arteries since they are often normal. Narrowing of the ostia of the coronary arteries is quite common, though the heart in failure is most commonly hypertrophied. It is thus seen that, excluding the cases in which congestive failure is due to an inflammatory or toxic process, the heart in failure

is, in the majority of instances, a hypertrophied heart. There is a common background for congestive heart failure of all types. The hypertensive heart in hypertrophy and failure appears to us to follow these common dynamic laws.

Increased diastolic length or tension is a significant, though not the sole, cause of cardiac hypertrophy. In severe anemia and in a considerable number of cases of essential hypertension, in which chronic increases of diastolic length may be assumed, hypertrophy does not develop. In extensive myocardial infarction, greater diastolic fiber stretching may also occur from primary loss of contractility. Though this type of case on physiological grounds could conceivably lead to cardiac hypertrophy, the production of increase in cardiac mass solely from coronary disease or myocardial infarction alone has not been substantiated clinically. Furthermore, despite primary loss of contractile power, congestive heart failure is uncommon in small hearts. The factor preventing hypertrophy in the exceptionally small heart in failure is unknown. Evidently, an additional factor must be present to produce increased cardiac mass. However, in the vast majority of cases without cardiac hypertrophy, congestive heart failure does not appear. The clinical implication of this fact is that even in the presence of major coronary artery disease, the hypertensive heart which is not greatly enlarged frequently does not go into failure.

*Anoxemia.*—Starling and Visscher[42] showed that the energy of contraction of a fiber is proportional to diastolic fiber length. Hemingway and Fee[43] observed a direct linear relationship between the diastolic volume and oxygen consumption. Evans and Matsuoka[44] stated that with a constant output, the work of the heart is proportional to, and increases up to, a maximum arterial pressure beyond which the heart fails. However, with low oxygen content, Jarisch and Wastl[45] noted cardiac dilatation, proportional, according to Van Liere,[46] to the degree of anoxemia. In other words, while oxygen consumption is proportional to diastolic length or dilatation, the dilated heart needs more oxygen to pump a given amount of blood.

In experimental tachycardia produced by mechanical means, and from hyperthyroidism, Menne, Jones, and Jones[47] observed a parallelism between the increased heart rate and the myocardial lesions. Buechner and von Lucadou[48] demonstrated disseminated necroses in animals exercised after bleeding and in animals not bled but severely strained. Rosin[49] showed marked fatty infiltration of the myocardium from diminished oxygen concentration. In chronic severe anemia in which anoxemia may be assumed, tigering and fatty infiltration occur.

Hill[50] demonstrated that the rate of diffusion of oxygen varies inversely as the square of the distance to be traversed or, in other words, according to the thickness of the muscle fibers. Harrison[51] observed that the pulse rate of different animals varies roughly inversely as the thickness of the heart muscle fiber. However, in the hypertrophied

human heart, the pulse rate is not correspondingly slow. Since the mean head of pressure or oxygen tension in the capillary is the same, the part of the fiber near a capillary will receive oxygen while the innermost part of the fiber will receive a diminished supply. Patterson and Starling[52] showed that for a given minute volume, the oxygen consumption was greater per beat, but less per minute at slow than at fast pulse rates. It follows that when the fiber is thicker than normal, with diastole not prolonged and the pulse rate not proportionately diminished, some degree of anoxemia of the heart muscle must sooner or later develop. Evidently, hypertrophy, a compensatory mechanism, has in it, if progressive, the danger of resulting, sooner or later, in cardiac fatigue. Further proof of this fact is that normal hearts go into failure from very rapid rates, whereas enlarged hearts go into failure much sooner from merely slightly augmented heart rates. The appearance of congestive heart failure under these circumstances is probably related to anoxemia. Furthermore, anoxemia would also account for the development of myocardial fibrosis with and without coronary sclerosis without being dependent upon the latter. It is plausible that myocardial fibrosis would be greater, however, in massive hearts as well as in hearts with coronary disease.

*Additional factors.*—It was shown by Elias and Feller[53] that a contractile mechanism is present in the liver veins which bears directly upon the state of filling and the stroke volume of the heart. Indeed, the circulation in the hepatic veins may actually come to a standstill from a dilated right auricle. This mechanism may be of great significance in maintaining the dynamics of circulatory efficiency. It was also shown by Mautner[54] and his associates that the opening and closure of the liver veins was governed by the vagus and sympathetic nerves and by the interchange of fluid in the liver. The contraction of the diaphragm and the resulting effects on the intrathoracic and intra-abdominal pressure and the filling of the heart is another important dynamic factor in the circulation.

*Metabolic factors.*—It is impossible to answer just when, and for that matter why, hypertrophy ceases to continue and the heart, despite the physiological stimulus of dilatation, fails to undergo further hypertrophy. The anatomical changes do not offer an adequate explanation of chronic congestive heart failure. The physiological facts merely indicate the dynamic conditions involved in cardiac hypertrophy. Consideration of the metabolic factors may therefore be of great value.

Seecof et al[55] showed differences in creatine content of the right and left ventricles. Cowan[56] demonstrated decreased creatine content in the hypertrophied heart muscle. This was more marked in cases showing congestive failure. A conspicuous increase in carbon dioxide and dextrose consumption during ventricular fibrillation as compared to the normally beating heart was shown experimentally by Hooker

and Kehar.[57] Following coronary occlusion in animals, the infarcted heart, according to Himwich, Goldfarb, and Nahum,[58] loses appreciable glycogen, which appears in part as increased carbohydrate and lactic acid. Long and Evans,[59] studying rats suffering from induced tetany, demonstrated marked reduction of the glycogen content of both the heart and the gastrocnemius muscle. Following reduction of oxygen, the cardiac glycogen fell markedly. Low cardiac glycogen stood in close relationship to cardiac failure while anoxemic animals allowed to recover had marked rises of glycogen.

Herrmann, Decherd, and Schwab[60] confirmed the loss of creatine in heart failure and in experimental myocarditis and, in addition, a loss of glycogen in the infarcted rabbit and dog heart. Clark, Eggleton, and Eggleton[61] showed that the hydrolysis of phosphagen is the immediate source of the energy of the contraction of the heart. Phosphagen disappears faster from tortoise auricular strips deprived of oxygen if the heart is beating rhythmically than if it is quiescent. The demonstration by Cowan[56] of creatine diminution in cardiac hypertrophy which was greater in congestive heart failure lends credence to this attitude, and recently Herrmann and associates[60] have reported phosphocreatine disturbances in experimental congestive heart failure.

Since impairment of function of any tissue is on final analysis due to impaired exchange of oxygen and metabolites, these factors are also, on such final analysis, the cause of failure and replacement fibrosis in the human heart. This view is acceptable if by it we understand that insufficient oxygenation and lack of metabolites in hypertensive hearts are no more due solely to coronary disease than the failure of rheumatic or emphysema hearts is due solely to coronary disease.

On final analysis, it appears that the problem of myocardial failure in essential hypertension must resolve itself into the disturbed relationship between muscle fiber size and the volume of blood flow through the capillary bed.

Even in the presence of major coronary artery disease, the heart with fibers of normal thickness may be capable of a stroke volume of adequate contractility to maintain circulatory efficiency. Indeed, though these hearts show some diminution of cardiac reserve, chronic congestive heart failure occurs relatively uncommonly in the absence of additional factors, such as hypertension, tachycardia, toxemia, and anemia which may cause chronically increased diastolic length and tension. Failure occurs when hypertrophy ceases to develop despite increasing diastolic length. Anoxemia, at such times, or metabolic factors are probably the determining factors of congestive heart failure.

Coronary disease, per se, is rarely a sole cause of chronic congestive heart failure. In the presence of cardiac hypertrophy with minimal coronary arteriosclerosis, congestive heart failure does occur, even if

infrequently. The cases of failure with coronary disease show, in the overwhelming majority, varying but very considerable hypertrophy. In our material, the patients with severe coronary disease and failure did not show hypertrophy as massive as those in which coronary disease was minimal. Failure in those with severe coronary disease, when present, commonly did not exceed two years. The failure in many was more or less acute following sudden impairment of nutrition as by an additional coronary occlusion. Under such circumstances, primary loss of contractility does not result in preponderant additional cardiac hypertrophy, and congestive heart failure supervenes.

In the group with minimal coronary disease, however, despite the larger size of fiber, greater diastolic fiber length for a long time constitutes an adequate stimulus for additional cardiac hypertrophy. Apparently, an adequate vascular supply keeps pace with the increasing muscle mass. This is shown by the fact that the hearts with minimal coronary disease lived longer in congestive heart failure and their heart weights were greater than those of the cases with major coronary artery disease. Congestive heart failure in both types is, however, the end-result of the hypertrophied heart which is unable to undergo further hypertrophy. The hypertrophied fiber may, however, for a long time, work at optimum efficiency despite diminished vascularity. In an enormous heart with the individual fiber greatly stretched and thickened and the blood supply relatively and absolutely diminished, an additional impairment of nutrition such as a small vascular lesion, which in normal sized heart may produce no symptoms, may, in the massive heart, produce acute or terminal congestive heart failure.

Any factor interfering with the nutrition of the muscle fiber, be this primary as in an infection or toxemia, or secondary from anoxemia as in hypertrophy, severe coronary artery disease, anemia, or tachycardia, will impair the contractility of the muscle fiber. Such loss of contractility may produce acute and chronic congestive heart failure. In the disturbed metabolism of the individual muscle fiber, however, lies the ultimate cause of congestive heart failure.

## SUMMARY

1. Cardiac hypertrophy is the feature common to cases of congestive heart failure irrespective of the presence or absence of major coronary artery disease. The congestive heart failure associated with an inflammatory or toxic cardiac lesion is an exception to this rule.

2. In hypertrophied heart muscle, the development of surface irregularities of the muscle fibers and alterations in the nuclei appear to be a compensatory mechanism to increase the diffusing surfaces.

3. A decrease in capillary and arteriolar tree proportional to the volume of the muscle mass was observed.

4. Three types of muscle changes were observed in many cases:
a. Microscopic acute infarcts similar to those seen in major coronary occlusion.
b. A slow process of fiber dissolution or fatty degeneration.
c. Connective tissue replacement of myofibrillae by an insensible merging of the muscle fibers with connective tissue.

5. Anatomical, functional, and mechanical factors appear to play a rôle in myocardial fibrosis. This fibrosis is not directly dependent upon coronary sclerosis even in the presence of marked coronary disease. However, myocardial fibrosis appears to be related to anoxemia from whatever cause.

6. A collateral circulation, both intracardiac and extracardiac may play a rôle in preventing failure of the hypertrophied heart. Sinusoids were found to be increased in number and size in many hypertrophied hearts and under certain circumstances are probably intimately associated with the nourishment of the heart.

7. Congestive heart failure is due to coronary insufficiency only in the sense that impairment of nutrition and necrobiosis are, on final analysis, a function of blood supply in heart tissue as in any other tissue.

8. Congestive heart failure is the failure of the heart which fails to undergo further hypertrophy. The cause of failure lies in some disturbance other than the anatomical, though cardiac hypertrophy is the cardinal associated finding. Such hearts may be correlated with demonstrable metabolic disturbances which appear to be the ultimate cause of failure.

## ILLUSTRATIVE CASES

CASE 1.—No. 24032. A man, sixty years of age, a known diabetic for fifteen years; with coldness and blueness of the feet for five years and anginal seizures of two years' duration. Four months before admission, he developed an ulcer over the left heel. Three months later, an ulcer appeared on the posterior aspect of the left foot. Examination showed advanced peripheral arteriosclerosis, gangrene of the left third toe, and an ulcer of the left heel. After two months in the hospital, he was discharged improved. However, after being home several days, an ulcer appeared in the lateral aspect of the right heel and another on the second right toe and he was readmitted. Three weeks after his admission, he developed sharp precordial pain and dyspnea at rest and several days later, pulmonary congestion and peripheral edema, and he died suddenly.

Necropsy showed a heart weighing 510 gm., marked coronary arteriosclerosis, marked narrowing of the right coronary artery by a recent thrombus and severe stenosis of the left coronary, and partial occlusion of the anterior descending branch of the left coronary artery, fibrosis of the interventricular septum and apex of the left ventricle, and recent infarction of the posterior wall of the left ventricle. Microscopically, there was slight, but definite increase of sinusoids.

This case illustrates the fact that despite severe coronary arteriosclerosis and myocardial damage in a large heart, congestive heart failure may not occur till the advent of an additional burden, such as recent muscle or vessel damage.

CASE 2.—No. 21286. A man, seventy-three years of age, with a history of weakness of several years' duration, dyspnea, and precordial pain of one year's duration and paroxysmal nocturnal dyspnea of ten months' duration. Examination showed minimal congestive heart failure with hepatic and pulmonary congestion and slight ankle edema four months before death.

Necropsy showed a heart weighing 380 gm. and no cardiac hypertrophy. The coronary arteries were pipestem with reduction of the lumens of the left circumflex branch, occlusion of the left anterior descending branch and narrowing of the right coronary artery. There was an infarct at the apex of the left ventricle and marked fibrosis of the interventricular septum and right ventricle. Microscopic examination showed numerous sinusoids in the myocardium.

This case shows (1) the relatively uncommon development of congestive heart failure in the absence of cardiac hypertrophy, (2) the late and mild failure in a small heart despite extensive coronary disease, (3) the rôle of the sinusoids in nourishing the heart itself, and (4) that coronary disease per se does not cause cardiac hypertrophy.

CASE 3.—No. 11358R. A female, sixty-two years of age, was observed at Montefiore Hospital over a period of three years, with a history of edema of the legs and abdomen of four years' duration and progressive dyspnea on exertion, of three and one-half years' duration. The blood pressure was 218 systolic and 128 diastolic. The liver edge was felt four fingers below the costal margin; cardiac asthma appeared. A left hemiplegia developed which in part improved. She was admitted to the hospital nine times on account of myocardial insufficiency, headaches, epistaxis, nausea, and epigastric pain. She developed acute appendicitis two days before death, and died of peritonitis. The signs of congestive heart failure were minimal before death.

At necropsy, she was found to have generalized peritonitis. The heart weighed 750 gm. The orifices of the coronary arteries were slightly encroached upon by atheromatous plaques. The coronary arteries were thin and soft. There was a moderate number of minute microscopic scars. The sinusoids showed a moderate to marked increase.

This case indicates the long duration of congestive heart failure in a very large heart in the absence of major coronary artery disease. The microscopic scars may be attributed to anoxemia. The numerous sinusoids may have played a rôle in nourishing the heart and preventing additional cardiac insufficiency.

CASE 4.—No. 21791. A male forty-three years of age, with hypertension, known one year, dyspnea and choking on exertion, of fourteen months' duration, and multiple cerebral vascular insults. Death was due to a cerebral insult. There was no history of congestive heart failure.

Necropsy showed a heart weighing 550 gm., marked atheromatosis of the left anterior descending and transverse coronary arteries with marked reduction of the lumens, marked atheromatosis of the right coronary artery with an old occlusion and a fresh mural thrombus with partial occlusion, and a small scar in the posterior wall of the left ventricle. There were numerous microscopic scars and only slight increase of sinusoids.

This case is indicative of the fact that despite severe coronary artery disease in a large heart, congestive heart failure need not appear even in the presence of a fresh mural thrombus in the right coronary artery.

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# AURICULAR PAROXYSMAL TACHYCARDIA (POSSIBLY NOMOTOPIC) WITH VARIABLE AURICULOVENTRICULAR CONDUCTION TIME

## Study of a Case of Exceptional Duration with Gradual Slowing of the Heart Rate*

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AURICULAR paroxysmal tachycardia, although a very frequent disorder, presents few opportunities for cardiographic study, since many patients learn how to stop the seizures before distress or congestive changes appear. In any case, few attacks last sufficiently long to allow arrangements to be made for the taking of cardiographic records. Only four such tracings were obtained in a series of 1,200 cardiograms taken in our department over a period of four years. Paul White[1] has reported a series of 132 cases (82 females and 50 males); two-thirds showed no evidence of heart disease. He agrees, however, that the frequency of the condition is inaccurately represented in any statistical studies available at present. Lewis'[2] classical tracings illustrate the commencement and termination of short paroxysms or bursts of extrasystoles, analogous to those which appear before and after the attack.

The abruptness with which the tachycardia begins and ends is generally considered as a characteristic feature of the condition. Indeed, such a history is often the only means of differentiation from attacks of palpitation resulting from undue heart consciousness, not necessarily associated with great increase of the heart rate. When the patient is seen during an attack, suspicion of the presence of this type of disorder, or of auricular flutter, is aroused by a heart rate of 140 per minute or more, which fails to respond to rest in the recumbent posture for an adequate period, and where constitutional disorders, such as hyperthyroidism, toxemia, or anemia, can be definitely excluded. Cardiographically, a high degree of regularity is apparent, the auricular complex is distorted in form, but the ventricular component is usually unaltered.

An opportunity recently presented itself whereby we were enabled to study at leisure an attack of paroxysmal tachycardia of supraventricular origin which departed from the classical description as regards the duration of the attack, and the regularity and mode of its

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[1] Much abridged by Paul D. White, Boston. For further details, consult the author.

termination, but which presented the usual features of the condition in respect of the cardiographic findings, the sudden mode of onset of the paroxysms, and the secondary effects upon the circulation.

## CASE REPORT

The patient, V. L., a female, aged thirty-nine years, visited the hospital because of a smothered feeling on waking at night, and sharp pain in the precordium and the left arm. She gave a history of having been breathless for several days, and for three days she had been unable to lie down on this account. She stated further, that from time to time during this period there had been violent throbbing of the heart, at times so marked that she was unable to read the newspaper held before her. She always had a florid complexion although this had never been of a bluish hue until seven weeks previous. Her health had been remarkably good and free from any evidence of rheumatism. Her mother had died at sixty years of age from "heart trouble."

The first attack of the present nature had been experienced seventeen years before, when her eldest child was eighteen months old. Since then she had had many short attacks, the longest interval between them being five years. The space of two years had separated several others. In each instance she described the onset as being sudden but could not be as definite about the mode of cessation. Her weight had increased considerably during the twelve months prior to her present attack and she stated that she had been more short of breath since then.

On examination, she weighed 155 pounds; presented a full round countenance with obvious purplish cyanosis of the cheeks and lips; this blueness was less marked in the case of the extremities. No edema was detected. She talked and carried on her usual activities without distress, but cyanosis deepened perceptibly as soon as she assumed the recumbent position. Movement of considerable amplitude could be observed in the cervical veins on each side, but there was no obvious venous distention elsewhere. She had a few carious teeth. No other focal infection was detected.

Examination of the precordium revealed a diffuse pulsation of large amplitude, maximal at a point in the anterior axillary line 15 centimeters from the midsternum at the level of the 4th intercostal space. No vibrations were palpable. The apical sounds were loud, completely irregular, sharp and slapping in quality, with relative emphasis on the second sound. At the base this exaggeration was less definite, and a soft systolic murmur was audible at the pulmonary area, varying with respiration. No congestive features were apparent in the examination of the respiratory, renal, or abdominal systems. The liver edge was impalpable. The patient was diagnosed as suffering from auricular fibrillation and recommended for admission. She was not anxious to leave her home, however, and continued to attend as an out-patient for seven weeks. On all occasions after the first visit, she presented a similar appearance and was mildly distressed, but the pulse rate was now entirely regular, varying between 150 and 160, and the heart sounds had a tick-tack quality. Pulsus alternans was present and the blood pressure readings averaged, systolic, 150; diastolic, 110 millimeters of mercury.

After seven weeks' attendance at the out-patient department, showing tachycardia at each visit, she consented to enter hospital for closer observation (Aug. 25, 1935). Symptoms and signs were as previously noted. Observations were made on her blood to exclude an erythremia, with the following results: red blood cells, 4,720,000 per cubic millimeter; hemoglobin, 14.4 gm. per cent, 90 per cent normal; mean corpuscular vol., 72 cubic microns; mean corpuscular hemoglobin, $30 \times 10^{-12}$ gm.; mean corpuscular hemoglobin concentration, 43 per cent; color index, 0.9; white cells 9,500 per cubic millimeter.

*Other Findings.*—Level of fasting blood sugar, 79 milligrams per cent; degree of arterial oxygen saturation (Haldane method), 59 per cent; $CO_2$ combining power

of venous blood, 51 vols.; basal metabolism rate, plus 8 per cent; Wassermann and Kline tests, negative; temperature, normal except for one slight rise (to 100° F.) on the second day of the hospital stay.

A radiogram of the skull was normal. Attention was drawn to the unusual thickness of the cranial walls. A small degree of apical sepsis was present around two teeth.

The record of the changes in the diameters of the heart (as shown in teleradiograms) indicated progressive shrinkage in the transverse diameter of the organ especially affecting the right side, coincident with slowing of the heart rate. The pulse rate was recorded hourly, and revealed a marked fall in frequency during the hours of sleep, but never reaching below 90, while the maximum rate recorded during the waking hours was 160. After thirty-six days in bed the pulse rate had fallen to 80, where it remained in spite of increasing exercise, until the discharge of the patient from the hospital.

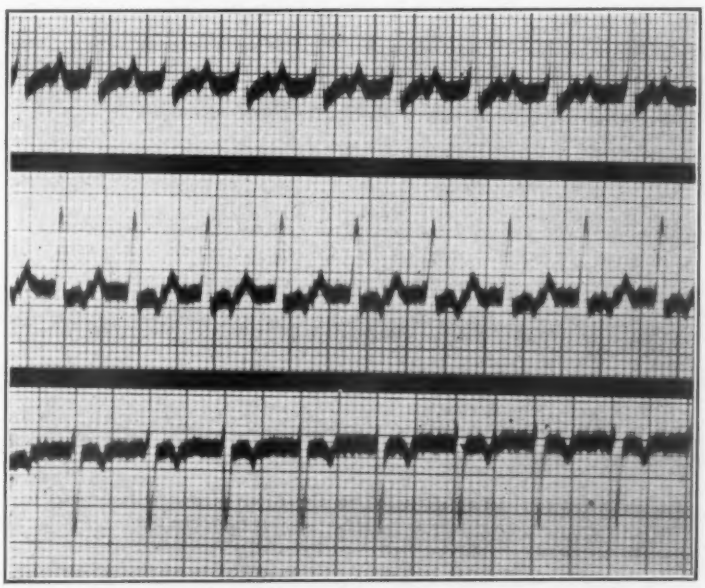

Fig. 1.—Initial tracing. All leads shown. The wave bears a distinct resemblance to that of nodal paroxysmal tachycardia, with a retrograde P-wave notching the upstroke of the T-wave. It was shown later, however, that the T-wave of Leads I and II is completely obscured by a bifid, aberrant, P-wave.

Reexamined on various occasions subsequently, the heart rate was consistently below 100 and the patient had experienced no further symptoms. The extraction of infected teeth, and an operation upon a septic thumb have since proved to be stimuli inadequate to initiate a further paroxysm.

Three months afterward (Dec. 23, 1935) the patient was sent for in the course of a routine follow-up. She arrived with a pulse rate of 168. She stated that she felt perfectly well. She had not been working hard, but had had a number of furuncles. No undue pulsation could be seen in the neck. The cardiogram showed sino-auricular tachycardia, in which no P-wave inversion appeared. The pulse slowed quickly on right carotid sinus pressure but no effect followed stimulation of the left carotid sinus.

## CARDIOGRAPHIC ANALYSIS

In all, some 30 cardiograms were obtained during a period of two months. The first curve, obtained on July 30, 1935 (Fig. 1), was

originally interpreted as showing nodal tachycardia with the auricular complex notching the T-wave of the same QRS complex, and the R-P interval measuring 0.16 sec. Dr. J. Crighton Bramwell, who saw this patient and tracing, agreed with a probable diagnosis of nodal tachycardia. Three days later, with the heart beating regularly at the same rate, i.e. 160, prolonged pressure was applied to the right carotid sinus. The presumed retrograde P-wave, hereafter called P′, was still visible (Fig. 2), but the curve as a whole was so flattened as to render further characteristics indistinguishable. The effect of this sinus stimulation was to render the pulse slightly slower and very irregular, with intermission of every third beat, the average time interval between the

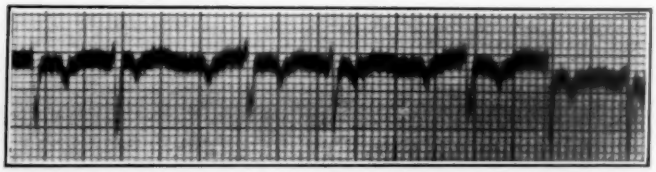

Fig. 2.—Lead III. Appearance on right carotid sinus pressure. Note regular appearance of bifid, aberrant, auricular complex, with single dropped beats at every third cycle.

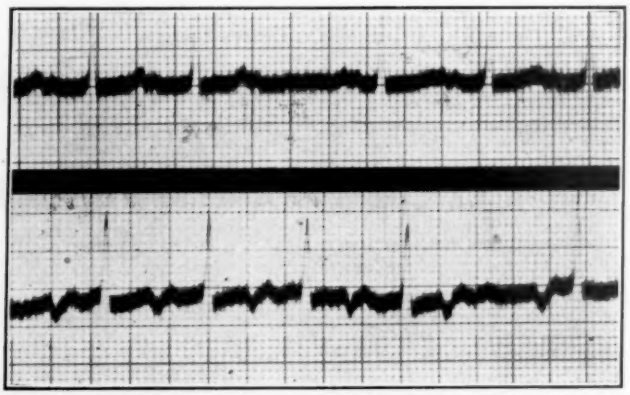

Fig. 3.—Leads I and II. Forty-five minutes after intravenous injection of digoxin 0.5 mg. Heart rate 120 per minute; conduction time progressively increased to 0.26 second just before a single missed beat occurs. The apparent T-wave in Lead I is then seen to be really a part of the deformed bifid auricular complex.

coupled beats being 0.48 sec. The groups of coupled beats were separated by a time interval of 0.72 sec. from each other in a remarkably constant manner.

The effect upon the cardiogram of intravenous injection of digoxin 0.5 mg. was next observed at intervals of 5, 15, 30, 45, and 60 minutes and compared with a cardiogram done immediately beforehand in which the heart rate was 150 per minute. Five minutes after the administration no changes were observable. Fifteen minutes later the pulse rate was 144 per minute. After thirty minutes the rate had decreased to 120. The P-waves of the second lead were still depressed. After forty-five minutes (Fig. 3) an interesting change had occurred;

the P′ had altered its form, the first upstroke being higher than the second instead of the reverse as previously, the curve almost resembling a simple tachycardia. What at first had looked like a T-wave, however, appeared even after a missed ventricular complex and hence must be part of the auricular wave. The P-R interval had increased progressively from 0.2 to 0.28 sec. at which point a ventricular complex was missing. The resulting long pauses were of consistent length throughout the cardiogram. One hour later a similar phenomenon was observable. $P_2$ had a duration of 0.12 sec., and like $P_3$, was inverted.

On Aug. 12, 1935, the patient, after half an hour's rest in the recumbent position, had a regular pulse rate of 56 per minute, but cardiographic analysis showed a 3:1 block and a conduction time of 0.2 sec. (Fig. 4). In this tracing it was possible to observe the exact character of the aberrant P-wave apart from any possible influence

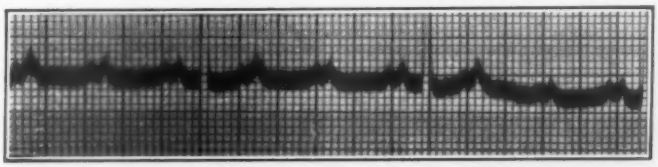

Fig. 4.—Lead I, with patient recumbent on Aug. 12, 1935, showing pulse rate of 56 due to 3:1 auriculoventricular block. The characters of the aberrant P-waves are here seen apart from any possible interference with T-waves. The influence of the latter deflection is to render the second peak of the P-wave higher than the first. It is on such appearances that all possibilities of a nodal tachycardia can be refuted.

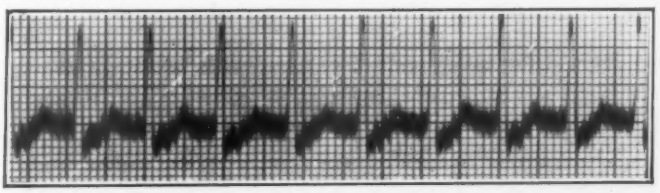

Fig. 5.—Lead II. Following exercise. Rate 170. There is no shortening of conduction time, so that the serrated auricular complex occurs immediately after the downstroke of the preceding S-wave.

upon it of the T-wave of a preceding ventricular complex. Its bifid form was preserved, and finally demonstrated that the apparent notching of T-waves which at first suggested nodal tachycardia, was illusory, and was due simply to the first deflection of the deformed auricular complex. On exercise the pulse rate rose suddenly to 168 while the conduction time remained 0.2 to 0.22 sec. (Fig. 5). Carotid pressure was then reapplied and the pulse became irregular with coupling. On release of the pressure the pulse again became regular with a 2:1 block. The effect of one gram of acetylcholine injected intravenously was studied at this juncture. The effect of this drug was to restore the rhythm of the pulse to a rate of 156 per minute.

With the patient sleeping under the influence of paraldehyde, and the pulse at 132, the conduction time was consistent in all leads, measuring 0.16 sec. The T-waves were flat throughout the whole of the

tracing. The absence of any intermission of the QRS complex, and the constancy and normal duration (0.16 sec.) of the conduction time are noteworthy features of these tracings taken during sleep.

By Sept. 20, 1935, the pulse had reached 96 per minute and it was now possible to see the P-wave separated by a distance of 0.24 sec. from the preceding T-wave (Fig. 6). The P-wave still maintained its bifid character in Lead I; was diphasic in Lead II, and inverted in Lead III. All S-T segments were depressed 1 to 2 mm. below the isoelectric level and marked left sided preponderance was present. Conduction time was now approximately 0.16 sec. Poorly marked T-waves were seen for the first time which were upright in Leads I and II, while no such waves were visible in Lead III. *In spite of what may be termed the cessation of the attack the abnormal features of the P-wave in all leads were maintained.* It is of interest that

Fig. 6.—Leads I, II, and III soon after fall of pulse rate to normal. Observe character of auricular complexes, still retaining somewhat the same form as during the paroxysm. Conduction time 0.2 second.

attempts to abolish the disturbance of rhythm in this case by quinine, guinidine, digitalis, acetylcholine, adrenalin, and atropine were all equally fruitless.

## DISCUSSION

This patient presents several departures from the classical description and usual criteria of auricular paroxysmal tachycardia. Even the question of nomenclature may be disputed. The patient, however, has had repeated attacks of tachycardia of a paroxysmal nature. They are not ventricular in type. At first the cardiogram was considered to represent a seizure of auriculoventricular nodal origin. The appearance of an aberrant P-wave in positions isolated from any ventricular deflections, and the absence of nodal extrasystoles immediately after the attack, throw reasonable doubt upon a genesis of ectopic impulse in the auriculoventricular node itself or its immediate neighborhood. The

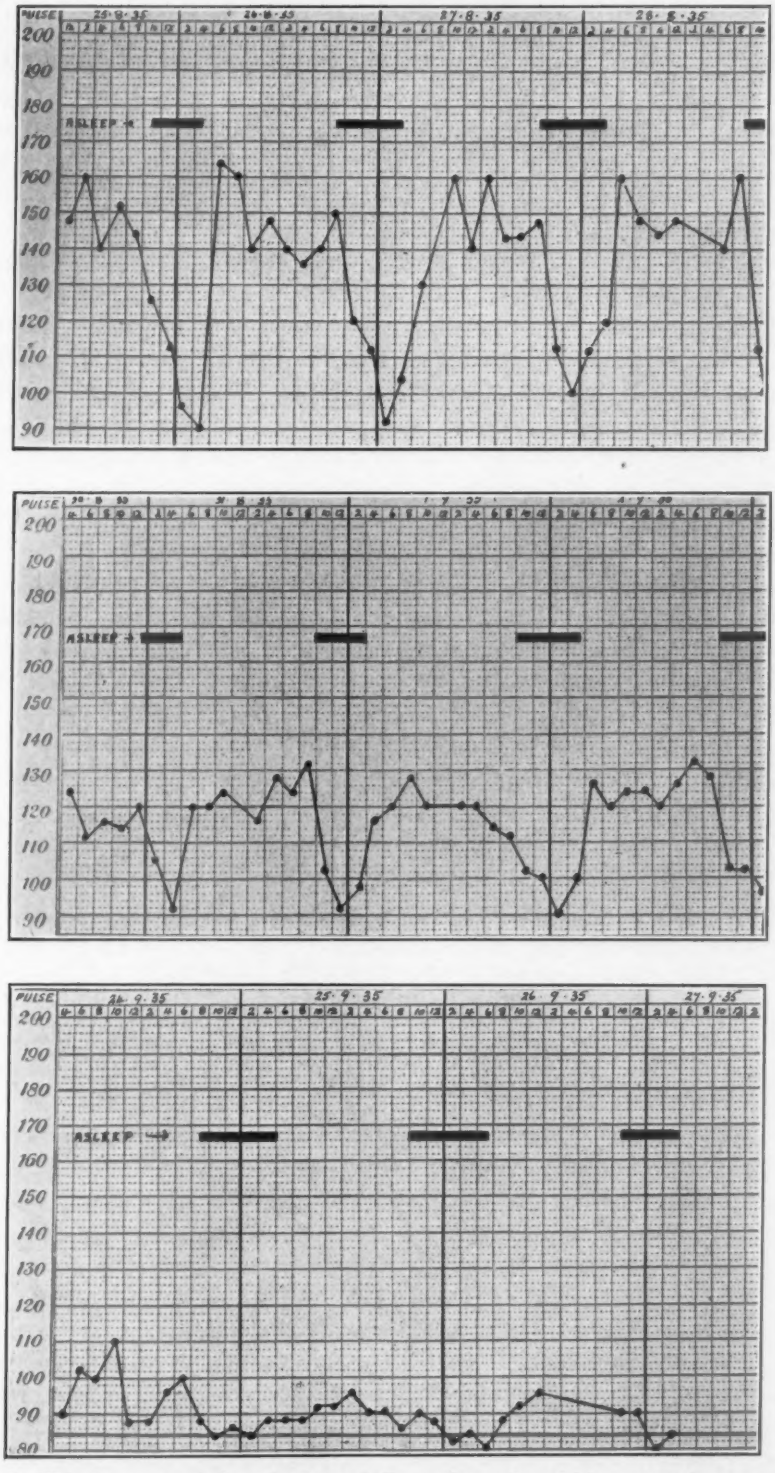


Fig. 7.—Showing progressive slowing of the pulse rate which approaches normal during the period of sleep, due to partial auriculoventricular block.

clinical and pathological associations, and the prognosis, of typical auricular and nodal tachycardia are so close, that from a practical viewpoint the distinction becomes confined to one of academic interest.

The locus of new impulse formation is of importance in relation to therapy directed toward abolition of the attack by stimulation of the vagus. After study of a patient exhibiting two irritable areas in the auricle, one near the auriculoventricular node, Carr[3] states that right carotid sinus stimulation will exert a greater effect upon nodal than upon sino-auricular rhythm. It is to be expected, however, that a tachycardia arising in or around the sino-auricular node would be more susceptible to right vagal influence. In Carr's patient, right carotid pressure caused ventricular standstill lasting 6.2 sec. In the present instance it was presumed that the new rhythm arose close to the normal pacemaker, as it was readily altered by stimulation of the right carotid sinus (Fig. 2), the P-R interval was equivalent to or even greater than normal, and the mode of termination, by lysis as it were, was of the nature usually represented by "nomotopic" tachycardia. The failure of vagal stimulation to diminish the heart rate and reestablish normal rhythm is perhaps due to the low grade of irritability of the cardiac muscle at the site of impulse formation and to continued depression after the actual vagal stimulation has ceased. Our chief difficulty is to reconcile the curious character of the new auricular complex with impulse formation at the sino-auricular node. One of the most constant criteria for a diagnosis of sino-auricular tachycardia is the preservation by the auricular complex of its normal configuration, and it has been held as axiomatic that an auricular complex of altered form denotes a site of impulse formation remote from the sino-auricular node, whether the arrhythmia is an extrasystole or a tachysystole. An isolated observation of Rothberger and Winterberg[4] is of interest in this regard. By stimulation of the peripheral sympathetic nerve supply to the heart on the left side, P-wave inversion appeared. In a heart rendered irritable by barium chloride, an attack of heterotopic paroxysmal tachycardia followed. It is a common experience, however, to observe, especially in the third lead, a negative or diphasic P-wave, in an otherwise completely normal tracing, and from an individual who is otherwise cardiologically sound. The particular alterations in the auricular complex in the patient under consideration, persisted long after the heart rate fell to under 100 per minute. Even weeks later, when the P-wave was again of the usual upright type, it was possible to detect a suggestion of its former deformity, especially in Lead III. Considered from this point of view, distortion of the auricular complex alone seems to be insufficient reason for excluding the presence of sino-auricular tachycardia. Boden[5] has described a patient in whom attacks of tachycardia occurred without any alteration whatever in the form of the P-wave or remainder of the curve—the pulse simply rising periodically

from 44 to 170 per minute. Galli[6] believes that attacks of "neurogenic" origin can arise in the normal pacemaker, and are more readily affected by vagal stimulation.

It is suggested that the patient under discussion in this paper suffers from a form of tachycardia in the genesis of which the extrinsic cardiac nerves take the major share. The reasons for this are that even during the height of the attack, emotion (such as on entering the hospital grounds), exercise, and sleep produced marked effects upon the rate and rhythm of the heart. Carotid sinus pressure failed to retard the auricular rate but produced a varying block.

A search of the literature reveals very little reference to attacks of paroxysmal tachycardia which are cardiographically heterotopic and yet which have a gradual, rather than an abrupt, ending. Marvin[7] has written an interesting account of a male arteriosclerotic patient whose first attack of ventricular tachycardia, with a rate of 174, subsided gradually over a period of eight days. The onset was sudden with oppression and palpitation. The subsequent occurrence of fever and leucocytosis and later of typical cardiographic changes of coronary occlusion of the $T_1$ type leave no doubt that this was the precipitating factor in his patient. A second attack of tachycardia ended abruptly, but a third required quinidine. Our patient is therefore most uncommon in this particular.

## SUMMARY

An attack of paroxysmal tachycardia in a female adult is described, which to our certain knowledge endured for sixty-nine days. The seizure was sudden in onset but gradual in decline. The cardiogram was typical of auricular paroxysmal tachycardia, but an unusual character of the auricular complex persisted for some time after the heart rate had returned to normal. This, together with the fact that the rhythm showed partial response to rest, exercise, emotion, and sleep, suggests that the case is of an intermediary character between nomotopic and heterotopic tachycardia.

I wish to express my thanks to my technician, Miss Scott, and to Dr. Crighton Bramwell and Professor C. G. Lambie for their encouragement.

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# PUBERTY AND PROGNOSIS IN RHEUMATIC FEVER*†

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THIS study is concerned with the relationship of age to susceptibility and resistance in rheumatic fever. It is based upon the study of a series of children who have been followed through childhood and adolescence; the age incidence of first and recurrent attacks of rheumatic fever has been recorded with a view to determine whether or not there is a period of life at which the recurrences become less frequent.

Primarily, rheumatic fever is not a disease of childhood per se if considered from the standpoint of the years of crippling morbidity which it may induce and the death rate. It is, however, a disease of childhood from the standpoint of the incidence of first attacks, for there is considerable evidence that, in urban populations at least, the majority of first attacks occur between the ages of five and twelve years.[1-6] Furthermore, although it is a disease which is subject to recurrences, there is also some evidence that if a primary attack has been sustained during childhood, recurrent attacks are more apt to arise during this period than later. Thus Swift[7] states that a condition of resistance seems to develop about the age of puberty. Willius[8] presents suggestive evidence that recurrent rheumatic infections are most frequent in the first decade of life and von Eickstedt[9] pointed out that reactivations occur less often after puberty. Stroud[10] has concluded that the primary manifestations and reactivations of rheumatic fever are more apt to occur between the ages of six and ten, and in a previous communication from this clinic[11] it was noted that after the age of seven years, recurrences decreased as age increased. The most extensive study of this subject is that of Wilson, Lingg, and Croxford[4] who, in a large series of cases, record fewer obvious recurrences after the ages of eleven or twelve years than before. The present study will deal with this decline in recurrent attacks which seems to occur at or shortly before puberty.

The clinical material available consisted of a group of 500 patients who had sustained one or more known attacks of rheumatic fever. All of them had been admitted to the New Haven Hospital or Dispensary at some time and most of them had been followed for several years in various cardiac clinics of the New Haven Dispensary.‡ The

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caliber of the material may differ from that described in previous similar studies in at least two respects: (1) the acquisition of rheumatic heart disease was not requisite for admission to the group, for many of the patients had had one or more attacks of rheumatic fever without detectable evidence of carditis; and (2) the patients were originally drawn from various clinics of a general hospital and not merely from a pediatric clinic—in other words, the age distribution of the group was not artificially weighted by a factor of selection on the basis of age.

Major criteria used for the diagnosis of active rheumatic fever in this group included the following manifestations: Sydenham's chorea, characteristic types of polyarthritis, subcutaneous nodules, and active rheumatic heart disease. Other signs and symptoms of supplementary value in determining the activity of the disease have included: erythema multiforme, frequent nosebleeds, otherwise unexplained fever and leucocytosis, and failure to gain weight.

It is well known that it is often difficult to determine accurately the age of onset of an attack of rheumatic fever. This is particularly true when the initial signs consist of growing pains or some of the supplementary diagnostic features mentioned above. We were, however, aided by one fact in making this determination, namely, that many of these patients had attended the New Haven Dispensary at intervals from the time of birth, and a more or less continuous record was available to supplement the story obtained at the time of an acute illness.

A recurrence has been defined as a period of activity of the disease occurring after eight to ten months or more of freedom from symptoms following a previous attack of rheumatic infection. For statistical purposes, only one attack per year has been included because of the difficulty of determining when one short attack has ended and another has begun if they occur within a period of a few weeks or months. In the rare instances when an attack lasted more than one year, the year of the onset only was included.

The ages of thirteen to fifteen inclusive have been chosen as the age period of puberty.

## RESULTS

*The Age Incidence of First Attacks.*—The ages at which members of the group of 500 patients sustained their first attacks of rheumatic fever and the ages at which heart disease was first detected are shown in Fig. 1. Three hundred and fifty-eight [71 per cent] developed rheumatic heart disease. This gives a fair idea of the caliber of the clinical material under observation with respect to age and the general severity of individual cases. It will be seen that, in accordance with the findings of other investigators, the highest incidence of initial attacks of

rheumatic fever in this group lies between the ages of five and eleven years. It will also be seen that there is a sharp drop both in the incidence of first attacks of rheumatic fever and also in the development of heart disease during the two or three years immediately preceding puberty.

*Age Incidence of Second and Third Attacks.*—One hundred of the patients have been studied more carefully. The criteria for their selection were: that the initial attack occurred before the thirteenth year of age; that there had been at least one recurrence; that they had been followed in the out-patient department or hospital for at least five years subsequent to the first attack; that they had been followed through the fourteenth year of life. Over 50 of these patients were followed for ten years subsequent to their initial infection.

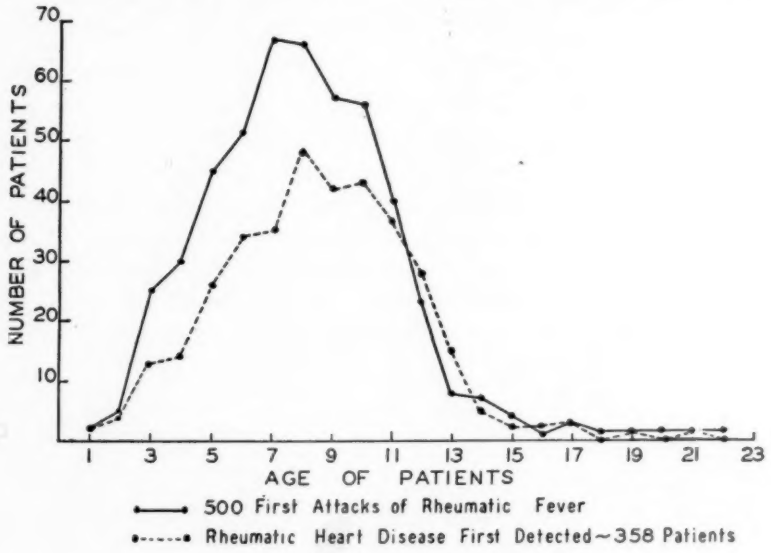


Fig. 1.

In Fig. 2 the relationship of first, second, and third attacks of rheumatic infection to the age of the patient is shown. As stated, all these patients had at least one recurrence; 60 of them had a second recurrence. It is to be noted that the period of greatest frequency of first recurrences falls between the ages of eight and thirteen years, and of second recurrences between nine and fourteen years. It is also apparent that a fairly sharp drop in frequency occurs for both second and third attacks between the thirteenth and fifteenth years.

From a study of these curves it is not clear whether or not this sharp decline in secondary and tertiary attacks, which occurs at about the age of fourteen years, is wholly dependent upon the age distribution of first attacks, for it is known that recurrences are more apt to follow shortly after a primary attack (i.e., within the first three to five

years[6]) than later. An alternative explanation is that regardless of the age of onset, this decline is an expression of gradually increasing resistance to the disease.

In an effort to secure further information relating to this question, the following analysis was made. Three groups of patients, who had

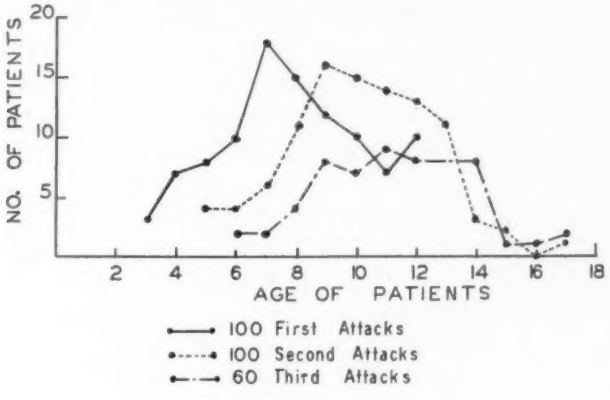


Fig. 2.

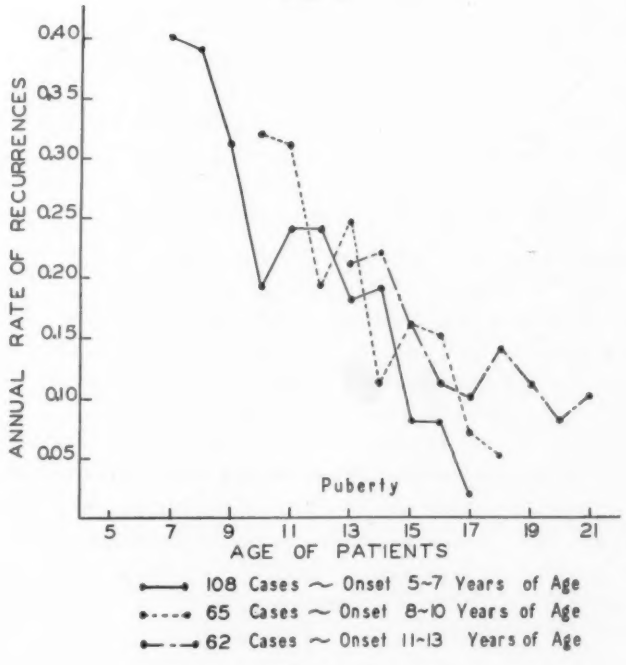


Fig. 3.

sustained their first attacks at different periods of childhood and who had been followed from five to thirteen years, were selected. The first attack occurred between the ages of five and seven years in 108 patients, between eight and ten years in 65 patients, and between eleven and thirteen years in 62 patients. In some cases a period of activity

during a given year has been estimated on the basis of history alone where physical examination was impossible; this has been recorded as one-half (0.5) a recurrence. The annual rate at which recurrences developed was determined in these three groups and is presented graphically in Fig. 3.

The curves here point to the fact that susceptibility (as judged by recurrent attacks) declines rather steadily as age increases over the period from seven to seventeen years. This decline, though definite, is quite gradual throughout this ten-year period. The configuration of the curves tends to minimize any sharp salutary effect upon the susceptibility to the disease which may come to pass during the age period of puberty, or one that is brought about by special physiological changes occurring at that time. They show, in other words, that the rates of recurrence are at least partly dependent upon the fact that a recurrence is more apt to follow close upon the heels of a primary attack than at some later time.

## COMMENT

It has been recorded in this paper that just as first attacks of rheumatic fever show a sharp decline in frequency preceding the age of puberty, so also do recurrent (second or third) attacks show a decline during or just after the same age period. Factors responsible for this decline will probably remain unknown as long as the pathogenesis of rheumatic fever remains obscure, but one may note two influences which seem to contribute to it; that is, two influences which lend themselves to some degree of analysis. One of these is the fact that inasmuch as there is a sharp decline in primary attacks before the age period of puberty, there will be a sharp decline in recurrent attacks during the years immediately following, for recurrent attacks are more apt to follow close upon the heels of a primary attack.[6] However, this is not entirely responsible for the improvement noted at puberty in this disease, for another contributing factor is apparent in the analysis of groups of patients who had sustained their first attacks at different periods of childhood. A gradual decrease in susceptibility occurs, which covers the ten-year period following the ages of seven to nine years. These two factors then, and possibly others, chance to coincide at about the age of puberty to cause a distinct lessening of the number of recurrences.

The recognition of this improvement at the age of puberty is of some value in prognosis.

## SUMMARY

The attempt has been made in this paper to analyze factors which bring about a sharp decline in recurrences of rheumatic fever at or about the age period of puberty.

Knowledge of the mechanism of this decline in susceptibility is limited, but two probable contributing factors have been noted and discussed.

Regardless of the mechanisms at work, the knowledge that improvement often occurs at puberty is of practical value in estimating the prognosis in rheumatic fever.

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# EFFECTS OF EPINEPHRINE ON THE HEART*

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EPINEPHRINE, in its action upon the heart, has a reputedly anomalous effect. Direct observations by Ducret,[1] on surviving vessel strips, disclosed that dilatation resulted from the application of a 1:100,000 solution of epinephrine. This author observed no reversal of the effect and he observed that a load on the vessel strip accentuated the epinephrine effect. Increased alkalinity diminished the response and increased acidity caused spontaneous dilatation. A temperature drop of one degree resulted in a decrease in the dilating effect of the epinephrine. This work is confirmatory of previous work on isolated coronary vessel strips.

Gollwitzer, Meier, and Krueger[2] on the basis of coronary flow experiments concluded that the sympathetics carry dilator fibers to the coronaries and that coronary dilatation follows the administration of epinephrine.

Klisiecki and Flek[3] studied the coronary flow with a photohemotachometer. Epinephrine, they concluded, acts as a vasoconstrictor on the coronary bed but this effect is nullified by the increased aortic pressure.

Anrep, Barsoum, and Talaat,[4] using the direct flow method on the coronary vessels, uniformly obtained an increase in the blood flow following the injection of epinephrine.

Melville[5] makes the following summarizing statement: ". . . coronary dilatation which undoubtedly follows the administration of many of these substances (ephedrine, adrenaline, histamine, and the nitrites)." This author presented further evidence of this effect by demonstrating that epinephrine and ephedrine are capable of abolishing the coronary constriction induced by posterior pituitary extract.[6]

The only direct observation on the heart following the administration of epinephrine was reported by Hurvitz and Smith.[7] These authors, in the course of experiments designed to study the effect of vasodilators following ligation of the coronary artery, found that the cyanosis which characterized the infarcted area was eradicated by the administration of theophylline. The cyanosis returned at once following the injection of 2 c.c. of 1:1,000 solution of epinephrine.

Electrocardiographic changes induced by epinephrine were described by Kahn[8] as directional changes in the T-wave. Later authors[9] de-

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scribed inversion of the QRS, "W" form of the QRS and elevation of the S-T interval following the injection of 1 c.c. of a 1:100,000 solution of epinephrine. Bartos and Burstein[10] observed inversion of the T-wave following the administration of 1 to 2 c.c. of a 1:100,000 solution of epinephrine, as well as following stimulation of the cerebral end of the cut vagus. Katz[11] induced precordial distress in two of six normal subjects following the administration of epinephrine. He precipitated moderate but typical pain and distress in two patients and a severe attack in a third case of known angina pectoris by the administration of this drug, substernal and precordial pain in a case of luetic aortitis and distress in an "irritable heart" subject. The electrocardiographic changes observed following the administration of epinephrine were chiefly downward deviation of the S-T interval and diminished amplitude of the T-wave.

Petzetakis[12] studied the effects of various sized doses of epinephrine in rabbits from the standpoint of the electrocardiographic changes induced. He noted slowing of rate following the administration of small doses of epinephrine intravenously. Larger doses induced extrasystoles, in addition to the bradycardia. As the dose was further increased this latter effect became more pronounced until lethal doses of epinephrine caused flutter or fibrillation of both the auricles and ventricles and bundle-branch block of varying degrees.

Stella[13] proved that the bradycardia induced by epinephrine is due to the effect of the blood pressure rise on the carotid sinus mechanism.

Anrep, Barsoum, and Talaat[4] demonstrated a marked increase in the histamine production by the myocardium, following the administration of epinephrine, independent of blood pressure, rate, or rhythm effects.

Frischi[14] demonstrated an increase in the water content of the myocardium after the administration of epinephrine.

Levy,[15] and Whitehead and Elliott,[16] demonstrated the increased capacity of epinephrine to induce ventricular fibrillation in animals under chloroform anesthesia.

Rosenblum, Hahn, and Levine[17] demonstrated an increased sensitivity of the heart to epinephrine after feeding thyroid extract.

Wiggers[18] states that epinephrine causes acceleration of conduction in the ventricles. The same author[19] states categorically that epinephrine causes constriction of the coronaries.

Angina pectoris, whether of spastic or sclerotic origin, is characterized from the electrocardiographic standpoint by either directional changes in the T-wave or deviation of the S-T interval from the isoelectric line, or both. These electrocardiographic changes are due to changes in the myocardium resulting in disturbances in the pathways of retreat.[20]

Similar changes have been brought about by anoxemia; Greene and Gilbert[21] caused shortening of the P-R and R-T intervals and decreased

amplitude or directional changes in the T-wave in normal humans by marked anoxemia. Kountz and Gruber,[22] and Kountz and Hammouda,[23] obtained similar results in experimental animals. Tigge[24] described as the characteristic changes induced in the human by reduced oxygen content of the inspired air an increased pulse rate, shortening of the P-R and R-T intervals, increased height of the P-wave, and flattening to inversion of the T-wave. These changes disappeared at once when adequate oxygen was supplied. Katz, Hamburger, and Schatz[25] carried out similar experiments with the same results. They were also able to induce more pronounced changes in four out of six cases of angina. The latter observation has also been made by Dietrich and Schweigk.[26] Pain was not a necessary accompaniment of the electrocardiographic changes so induced. Creip[27] observed directional changes in the T-wave and changes in level of the S-T interval during anaphylactic shock and postulated myocardial anoxemia as the cause. Anginal pain with inversion of the T-wave and displacement of the S-T interval was noted in the absence of pathological changes in the coronary vessels in a case of severe anemia by Elliot.[28]

## EXPERIMENTS

A series of experiments was designed to determine the mechanism of the epinephrine effects on the heart as indicated by the changes induced in the electrocardiogram.

The general procedure included the comparative effect of injection of epinephrine into a systemic vein and a coronary artery as well as the effect of epinephrine before and after vagotomy.

Dogs were anesthetized with nembutal administered intraperitoneally. The coronary artery was exposed in the following manner for the intracoronary injection:

A curved incision with the convexity toward the midline was made extending from a point about 1 cm. caudad to the apex beat to the level of the fourth rib. The pectoral muscles were divided between clamps, two or three ribs were severed, and the pleural cavity opened. A respiratory pump connected with the trachea was started at this point.

The pericardial sac was opened and tension on its edges served to lift the heart into the field. The epicardium overlying the anterior descending branch of the coronary artery was grasped with mosquito forceps and divided, exposing the vessel. Injections were made through a 26 gauge needle. The bleeding which occurred after the withdrawal of the needle was controlled by pressure applied for a few moments over the bleeding point.

Electrocardiograms were made using Lead II, before, during, and at intervals after the injections. Control tracings were made after inserting the needle and after injecting normal saline. In some of the experiments simultaneous carotid pulse tracings were made by means of a Hürthle manometer whose arm threw its shadow on the camera slit of the electrocardiograph. The following dilutions of epinephrine were used: 1:250,000; 1:50,000; 1:25,000; 1:10,000 and 1:1,000. Rather wide variations in the degree of response were encountered in the individual animals. Qualitatively, however, the changes were uniform. An electrocardiogram from each group displaying the characteristic, marked changes will be described in detail.

**Experiment IX. 1:250,000 solution of epinephrine (Fig. 1.).**

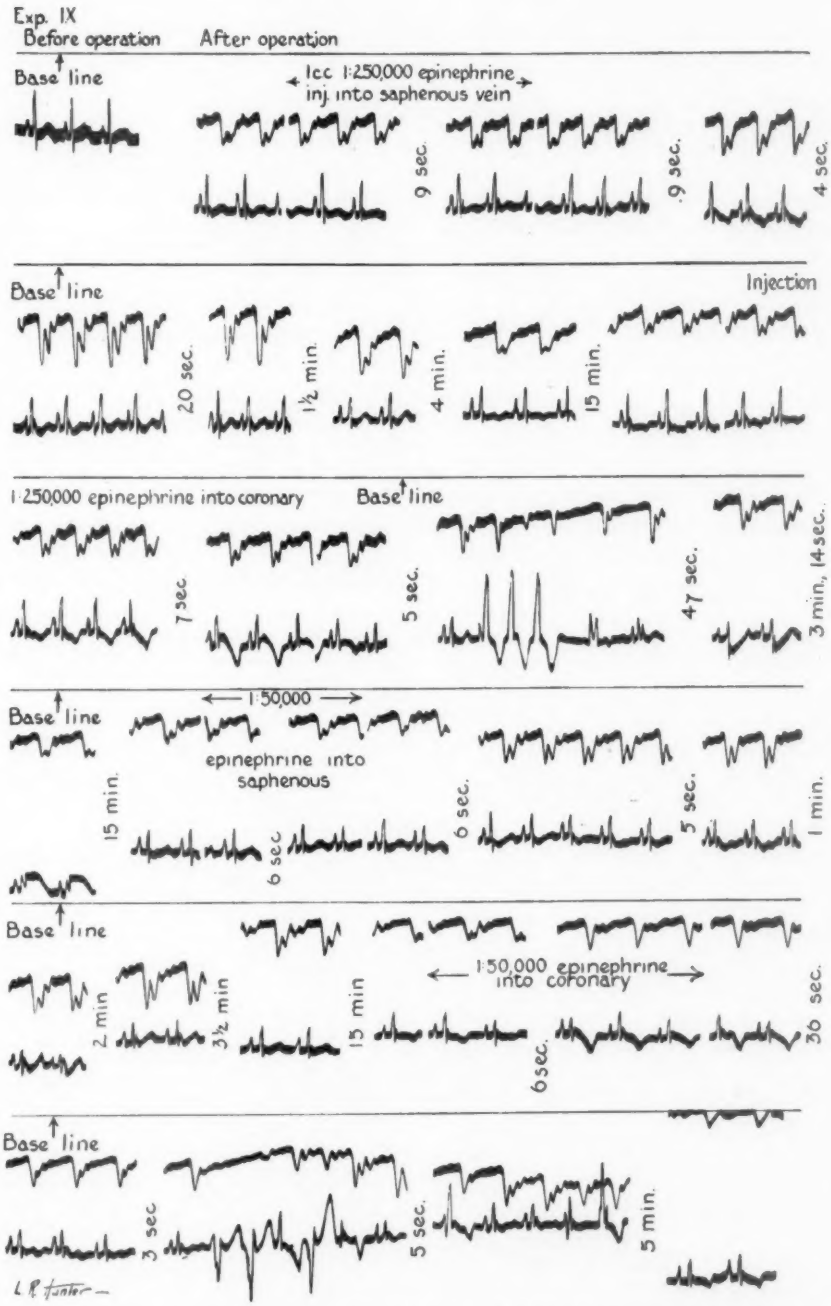


**Fig. 1.—One cubic centimeter of 1:250,000 and 1:50,000 solution of epinephrine each injected into the saphenous vein and the coronary artery. Note that pulse tracing is inverted.**

In the control tracing the PQR was normal, the S was rather deep, and the T, upright. A second tracing was made immediately after the chest was opened and the carotid incannulated. The T-wave had become isoelectric. There were no variations in the pulse record.

One cubic centimeter of 1:250,000 solution of epinephrine was injected into the saphenous vein during a period of seventeen seconds. The blood pressure began to rise twenty seconds after the completion of the injection. Three seconds later the T-wave became diphasic for several beats and then definitely inverted. The S-T interval became depressed, arising from an elevated take-off; the T again became diphasic but the S-T interval remained depressed during the succeeding one-half minute. The pulse curve heralded these changes by a gradual increase in diastolic and systolic pressures. After fifteen seconds, the diastolic pressure had returned to its original level and during the succeeding beats dropped below it. The systolic pressure, however, continued at the maximum level or only slightly below. The primary oscillations of the injection phase became more prominent and more sharply separated. The rate increased from 120 to 140 during this period. The electrocardiographic tracing continued to display a high T-wave with a depressed S-T during the succeeding two minutes; it then became diphasic and finally inverted. The pulse wave gradually returned to its original level and configuration.

Ten minutes after the first injection 1 c.c. of 1:250,000 epinephrine solution was injected into the coronary artery over a period of sixteen seconds. Within a few beats after the injection was begun the blood pressure began to rise and simultaneously the milliamperage of the already inverted T-wave began to increase and its take-off became elevated, both features becoming very pronounced before the injection was completed. After the completion of the injection the T-wave became diphasic for a few beats and then upright from a depressed take-off.

The pulse curve showed little change other than a moderate elevation in pressure. This returned to the original level fourteen seconds after the completion of the injection. At this point a series of three ventricular extrasystoles was recorded, followed by a notched R-wave and an inverted T. The T-wave then became upright. The pulse tracing displayed single small ejection waves corresponding to the ventricular extrasystoles and a drop in the pressure level during this period.

Seconds later the take-off of the T-wave became markedly depressed. Five minutes after the injection was completed the S-T interval rose to a point above the isoelectric line. This lasted for another minute when the T-wave again became depressed.

A second injection of 1 c.c. of 1:250,000 epinephrine was made into the coronary artery over a period of fourteen seconds. An elevated take-off to a deeply inverted T-wave developed during the injection, gradually becoming less and less prominent during the subsequent four seconds, then three ventricular extrasystoles occurred followed by a series of waves characterized by an elevated S-T convex to an inverted T. A single ventricular wave was interpolated into this group. Gradually the S-T segment dropped, the T remained inverted. The blood pressure rose during the injection. After its completion the pulse waves became less prominent and, corresponding to the first ventricular extrasystoles, the blood pressure dropped sharply, remaining at a low level for fourteen seconds when it again rose to a point slightly above its previous level.

During the subsequent five minutes the S-T interval remained elevated, rising convexly to an inverted T-wave.

After another few minutes the S-T returned to the isoelectric line and the T became upright.

One cubic centimeter of 1:50,000 epinephrine was injected into the saphenous vein over a period of fourteen seconds. Twenty-three seconds after the completion of the injection the blood pressure began to rise and the amplitude of the T-wave

increased slightly for a few beats. The T-wave then became diphasic for twelve seconds, then upright and its amplitude increased. The S-T interval was depressed and concave to an upright T. This gradually disappeared in the next four minutes leaving an upright T of low amplitude.

One cubic centimeter of 1:50,000 epinephrine was injected into the coronary artery over a period of twenty-one seconds. Prior to the injection, T was inverted and of small amplitude. Its amplitude began to increase, the take-off began to rise and the S-T interval became convex during the period in which the injection was being made. Simultaneously with the first change in the T-wave the blood pressure rose slightly but returned to its original level before the injection had been completed. The pulse curve began to change simultaneously with the rise in pressure and soon was characterized by a single clean-cut upthrust of the ejection phase followed by a series of small oscillations. Six seconds after the completion of the injection the pressure again began to rise and corresponding to this the amplitude of the T-wave became less. Forty seconds later the T-wave became diphasic, followed by a series of ventricular extrasystoles associated with a drop in blood pressure. With their passage the blood pressure again rose. These changes were followed by an irregular series of beats with upright, inverted and diphasic T-waves and ventricular extrasystoles. This persisted for a minute when the tracings again became regular with a small inverted T-wave. The blood pressure, after four minutes, began to fall, reaching a level much lower than the original.

One cubic centimeter of 1:10,000 epinephrine was injected into the saphenous vein over a period of 18 seconds. Twenty seconds after the completion of the injection the blood pressure began to rise and the previously low amplitude T-wave increased, and the S-T interval became depressed and concave. T soon became diphasic. Forty-five seconds after the completion of the injection a series of ventricular extrasystoles occurred followed by ventricular fibrillation.

Experiment V. Control: Rate, 178; P, 0.3 mv.; T, upright; 0.2 mv.

One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of twenty-three seconds. Five seconds after the injection had begun T and P began to approach each other so the T-P interval became "V" shaped with the apex above the isoelectric line. This became more pronounced so that nine seconds after the injection was begun T and P formed an "M" shaped curve. The voltage of the T-wave gradually diminished and it became diphasic with its initial deflection downward. The rate had increased to 210. This curve persisted for about a minute. Two and one-half minutes after the injection had been completed the T had become upright again and two minutes later the curve had returned to its original configuration.

One cubic centimeter of 1:10,000 epinephrine was now injected into the saphenous vein during a period of six seconds. The resulting changes in the curve were similar to those described above but quantitatively more marked. These changes persisted several minutes longer than after the first injection.

Experiment VI. Control: Rate, 170 (Fig. 2).

Configuration normal. Isolation of the coronary artery and insertion of the needle caused a slight increase in voltage of T and P and the rate increased to 176.

One cubic centimeter of 1:25,000 epinephrine solution was injected into the anterior descending branch of the left coronary artery over a period of fifteen seconds. Nine seconds after the injection was begun notching of the R-wave developed and the voltage of the T-wave began to increase. The T-wave became irregular in that its outline varied and the level of the S-T interval varied. This type of curve persisted for thirty seconds and then gradually returned to normal one minute after the completion of the injection. During another minute occasional "W" shaped R-waves occurred. The maximum rate was 175.

Control: Upright, T; normal configuration; Rate, 93.

One cubic centimeter of 1:10,000 solution of epinephrine was injected into the saphenous vein over a period of 19 seconds during which time the blood pressure and cardiographic curves remained unchanged. Eight and two-tenths seconds after completing the injection three ventricular extrasystoles occurred during which the pulse pressure was diminished. Twenty-three seconds after the completion of the injection the T-wave became diphasic and two beats later definitely became inverted and the S-T interval depressed. Corresponding to the first changes in the T-wave the systolic, diastolic, and pulse pressures rose. This phase lasted five seconds.

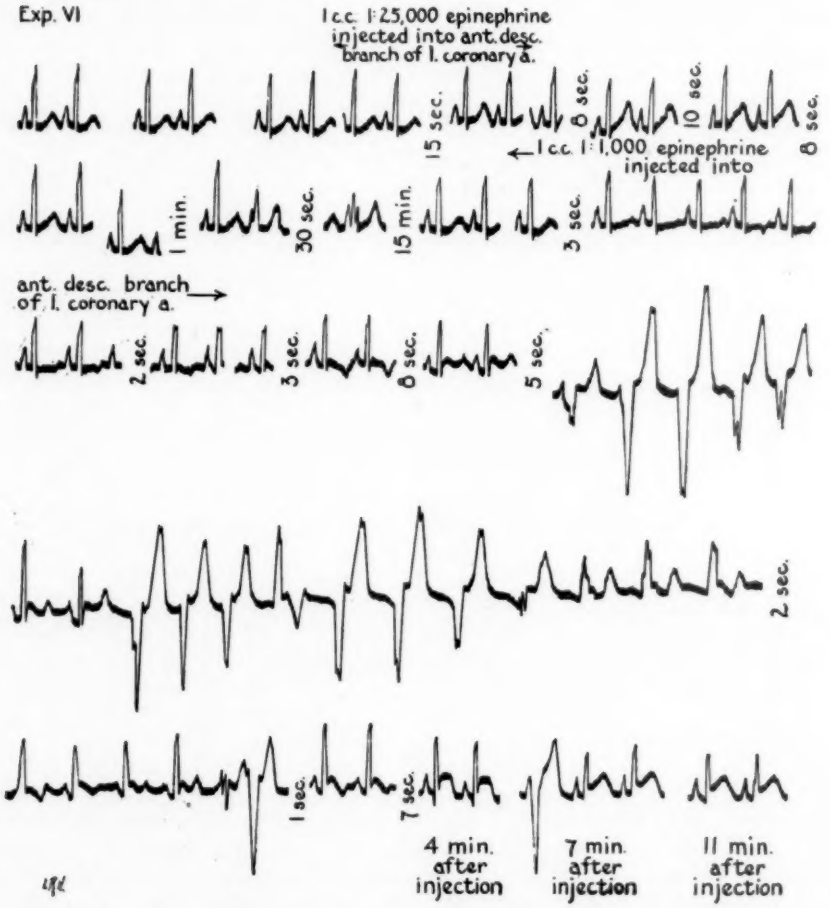


Fig. 2.—One cubic centimeter of 1:25,000 epinephrine solution injected into the saphenous vein and the coronary artery.

During the succeeding seven seconds the systolic and diastolic pressures continued to rise but the pulse pressure diminished. The electrocardiogram continued to display an inverted T and depression of the S-T interval. There then occurred a series of ventricular contractions characterized by a prominent QRS and a deeply inverted T-wave lasting six and one-half seconds during which time only one auricular contraction was recorded. Except for a beat corresponding to the auricular contraction the carotid pulse curve failed to show a pulse wave, and, except for a small rise soon after the onset of the ventricular complex, the blood pressure dropped.

The rate now became somewhat slower, and, corresponding to the return of the P-wave, pulse waves were again recorded. The T-waves remained inverted and of varying but usually high voltage. P-waves came through at irregular intervals. The systolic, diastolic, and pulse pressures increased and the rate dropped to 55. A pause, lasting two seconds, was followed by a complete cycle with a diphasic P-wave. The pulse curve was variable but was maintained with an increased systolic, diastolic and pulse pressure.

After an interval of several minutes the pulse curve had returned to the original level.

One-half cubic centimeter of 1:10,000 solution of epinephrine was injected into the coronary artery. Three seconds after the completion of the injection a ventricular extrasystole occurred associated with a drop in blood pressure. This wave did not come through on the pulse curve. The succeeding beats could not be interpreted in the cardiograph because of the extrinsic interference until twenty-five and one-half seconds after the injection had been completed when the T-wave became diphasic, then inverted for a few beats, and again diphasic. This curve persisted for several minutes. The pulse curve remained unchanged throughout.

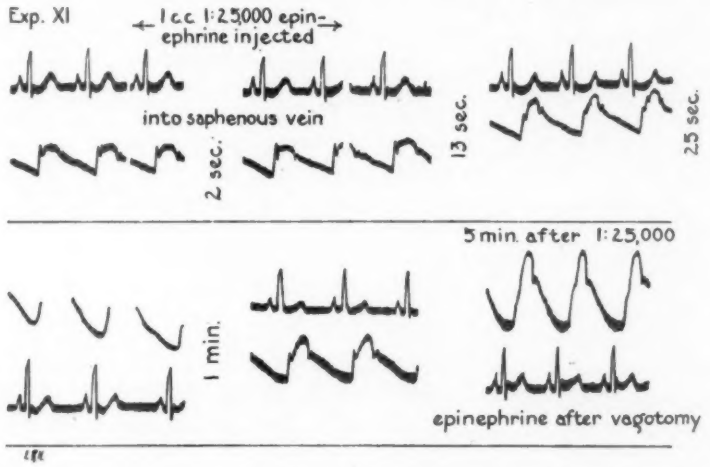


Fig. 3.—One cubic centimeter of 1:25,000 solution of epinephrine injected into the saphenous vein before and after vagotomy.

Experiment VIII. Control: Rate, 170; T, upright; configuration normal.

One cubic centimeter of 1:1,000 epinephrine solution was injected into the saphenous vein during a period of six seconds. At the completion of the injection the rate increased to 200 for several beats and the T-wave became isoelectric. The rate then slowed and the T became upright and of increasing voltage. The P-R interval varied from 0.08 second to 0.40 second and R became notched. The rate then stabilized at 75. At this time the T-wave was of high voltage and the P-wave was absent. This continued for one minute. The rate then rose rapidly, the QRS became inverted and the upright T increased in voltage to over 1 mv. and no P-waves were recorded. The rate stabilized for a minute at 235 to 260. Four minutes after the completion of the injection the rate was 270, the QRS was inverted, the S-T interval elevated, T upright and of moderate voltage, and no P-wave was apparent. A minute later R was again upright, S-T elevated, and T of low voltage. During the succeeding three minutes T again increased and R diminished in voltage. At the end of this period a series of bizarre ventricular waves was recorded, followed by another series of ventricular complexes lasting about forty-five seconds and charac-

terized by inversion of QRS and a high voltage upright T-wave. These gave way to a series having an upright R of rather low voltage and an upright T. Gradually the rate slowed to 157, and the P-wave reappeared. R was still of low voltage and S-T was elevated. Ten minutes after the injection the rate was 140, P present, R of low voltage, and S-T slightly elevated.

Experiment XI. Control: Rate, 103; P, 0.4 mv.; Q, obscure; R-Q mv.; S, deep; S-T, depressed 0.05 mv.; T, 4.5 mv. (Fig. 3).

One cubic centimeter of 1:50,000 solution of epinephrine was injected into the saphenous vein over a period of seventeen seconds. During the last seconds of injection the blood pressure began to rise but shifting of the string prevented any accurate judgment of the electrocardiogram. Five seconds after the injection S-T was isoelectric and T was 5 mv. The rate was 93. The T-wave was still at 5 mv. at the end of fifteen minutes and the S-T interval had returned to a level slightly below the isoelectric line when 1 c.c. of 1:25,000 epinephrine was injected into the saphenous vein over a period of sixteen seconds. Six seconds after the completion of the injection the blood pressure began to rise. Ten seconds later the S-T interval became definitely depressed. Save for a few long beats the rate remained unchanged. The T-wave decreased to 0.3 mv.

Four minutes later the curve had entirely recovered its original configuration.

The vagi were cut and 1 c.c. of 1:25,000 epinephrine was injected into the saphenous vein. Due to technical difficulties only a short electrocardiogram was obtained several seconds later. This showed the S-T interval to be elevated and concave to an upright T. The S-T was isoelectric for several minutes but the T was the shape of a broadened and flattened "M."

One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of twelve seconds. The blood pressure began to rise thirteen seconds after the completion of the injection and during the succeeding ten seconds the voltage of the T-wave diminished and twenty-five seconds after the injection the previously broad, flat "M" form of the T-wave disappeared leaving the usual type of wave. The S-T interval became depressed during this period. Ten seconds later the T-wave became diphasic, then inverted, then diphasic again, and finally upright, during a period of thirteen seconds. During the succeeding forty-six seconds the voltage of the T-wave diminished and the blood pressure reached its maximum as did the pulse pressure. At the end of this period the T-wave was isoelectric. This persisted for a few beats when a very small inverted T-wave could be discerned becoming more prominent, and gradually becoming upright with an elevated S-T interval. Fifteen minutes after the injection the T-wave had resumed its broad, flat "M" form.

Experiment X. Control: Rate, 203; P, 0.5 mv. 0.04 second; P-Q, 0.04 second; Q, inconspicuous; R, 0.7 mv. 0.02 second; S, prominent 0.3 mv.; S-T, isoelectric 0.04 second; T, upright 0.5 mv. 0.06 second (Fig. 4).

Pulse wave—pressure constant. One cubic centimeter of 1:50,000 solution epinephrine was injected into the saphenous vein over a period of thirteen seconds. No change followed this injection.

One cubic centimeter of 1:25,000 solution epinephrine was injected into the saphenous vein over a period of thirty seconds. The diastolic pressure rose slightly at the completion of the injection as did the systolic. The T-wave became diphasic three seconds after completion of the injection and inverted 6 beats later. The blood pressure began to rise three seconds after the T-wave became diphasic. The T-wave remained inverted for twenty-two seconds when it became diphasic for four and one-half seconds. During this period the blood pressure had reached and maintained a very high level. The T-wave turned upright with a sharp apex. Its voltage gradually increased corresponding to a slight drop in the blood pressure,

reaching a maximum of 0.7 mv. in contrast to the preinjection level of 0.4 mv. The increased voltage of the T-wave persisted during the succeeding five minutes. The pulse rate decreased from a preinjection rate of 225 to 214, six seconds after the injection had been completed. During the succeeding ten minutes the T-wave remained somewhat elevated and the T-P interval took on an "M" form.

A second injection of 1 c.c. of 1:25,000 epinephrine into the saphenous vein over a period of fifteen seconds resulted in a transient diphasic T coming on five seconds after the completion of the injection corresponding to the beginning of the blood pressure rise. The diphasic T was replaced after two seconds by a depressed S-T interval. Simultaneously the voltage of the T-wave began to increase reaching a maximum of 0.7 mv. During the succeeding ten minutes the preinjection configuration of the blood pressure curve returned.

The vagi were cut without altering the configuration. The rate rose from 220 to 235. One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of seventeen seconds. The blood pressure began to rise shortly before the end of the injection. Three seconds after the injection was completed

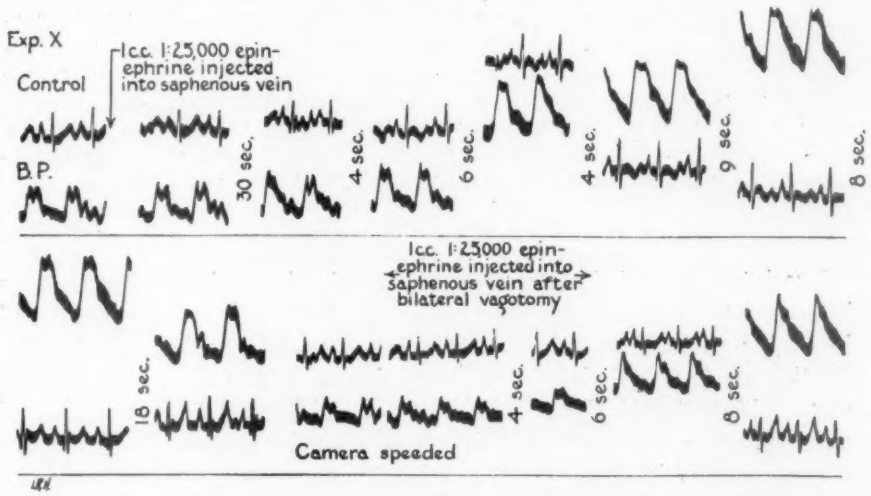


Fig. 4.—One cubic centimeter of 1:25,000 solution of epinephrine injected into the saphenous vein before and after vagotomy.

the T-wave became diphasic, remaining so for nine seconds when the S-T interval became depressed and the height of the T-wave began to increase. T-P took on an "M" form at this time. The configuration was gradually modified during the succeeding ten seconds until the T-wave reached a maximum of 0.7 mv., the S-T interval remained depressed and the T-P interval returned to the isoelectric line. The rate rose to 253.

Experiment XII. Control: Rate, 140; P, 4.5 mv.; Q, inconspicuous; R, 1.5 mv.; T, inverted.

One cubic centimeter of 1:50,000 epinephrine was injected into the saphenous vein. Eleven seconds after the beginning of the injection the form of the pulse wave developed a sharp, short ejection phase, and a drop in the pulse pressure and the systolic and diastolic blood pressures occurred. Corresponding to this the T- and P-waves became isoelectric, the latter reappearing after a few beats. The T-wave reappeared diphasic and then became upright corresponding to a rising diastolic, systolic, and pulse pressure. With the reappearance of the P-wave the pulse curve changed and the ejection phase became broader. After another fifteen

seconds the T-wave again became diphasic and then over another fifteen-second period inverted with an increasing voltage. Nine minutes after the injection the curve had returned to the configuration seen in the control.

Cutting the vagi resulted in a momentary pause but no subsequent change in the curves.

Strong vagal stimulation for 5.5 seconds stopped the heart momentarily. This was followed by a few slow beats with a marked increase in the voltage of the inverted T-wave. Mild vagal stimulation caused a marked decrease in the pulse waves and blood pressure but no change in the electrocardiogram.

One cubic centimeter of 1:50,000 epinephrine solution was injected into the saphenous vein over a period of nine seconds. The blood pressure rose slightly twenty-four seconds after the completion of the injection and, corresponding to this change, the S-T interval rose slightly and the voltage of the normally inverted T-wave diminished. Ten seconds after its initial rise the blood pressure dropped and the T-wave became diphasic for 8 beats, then upright for a few beats, again diphasic, inverted, diphasic, upright, isoelectric, and finally inverted.

After fifteen minutes 1 c.c. of 1:1,000 epinephrine solution was injected into the saphenous vein over a period of eight seconds. The T-wave became isoelectric five seconds after the completion of the injection corresponding to the beginning of the rise in blood pressure. At the same time the P-wave became markedly reduced in amplitude. The T-wave soon became inverted but the rate having increased to 200 the T and P were run together. The S-T interval rose and became convex to an inverted T and finally ventricular fibrillation set in.

## DISCUSSION

The intravenous injection of a solution of epinephrine causes changes in the electrocardiographic tracing closely simulating those encountered in angina pectoris in which condition the myocardium but not the conduction mechanism is involved. There is a wide variation in individual susceptibility to the drug both in human subjects and in experimental animals. The minimal effect is a reduction in the amplitude of the T-wave. This is closely followed by the appearance of the diphasic form. Next, directional changes in the T-wave, i.e., a previously upright T becomes inverted or vice versa, or a marked increase in the voltage of the T-wave appears. Deviation of the S-T interval from the isoelectric line is often associated with these pronounced changes in the T-wave. Finally ventricular extrasystoles and, with very large doses of epinephrine, ventricular fibrillation set in. With very large doses of epinephrine transient conduction interference may occur.

These changes were induced with much greater regularity and as would be expected, by much smaller doses when the drug was injected into the coronary artery than when the injection was made into the saphenous vein. When given by the coronary route even small doses of epinephrine caused transient notching of the R-wave in some instances.

In every tracing in which both were recorded the blood pressure rise occurred simultaneously with or immediately preceded the most minute changes in the electrocardiographic tracing.

Division of the vagi served to increase the epinephrine effect.

Coronary flow experiments indicate that epinephrine causes an increase in the volume of blood passing through the coronary vessels. It is hardly an acceptable hypothesis that this increased blood flow through the coronaries would cause the electrocardiographic changes recorded after the injection of epinephrine.

Though generalized oxygen lack causes changes in the ventricular complex its most characteristic effect is first to speed up A-V conduction and later to slow it, in contrast to the primary effect of epinephrine on the ventricular musculature and its minor effect on conduction. Thus if the epinephrine effects observed were dependent entirely, or even largely, upon diffuse coronary constriction they should simulate oxygen deprivation effects more closely.

The changes encountered can only be accounted for by the following train of events.

Epinephrine, by increasing the demand of the myocardium for blood far beyond the increased availability resulting from increased coronary blood flow, causes a relative or functional anemia of the myocardium. This results in changes in myocardial action comparable to those of a normally functioning myocardium which is having its blood supply diminished. Because the changes encountered develop so rapidly they must be the result of relative myocardial anoxemia.

The contrast between the effects of generalized anoxemia and those of epinephrine is then to be explained by the fact that during the epinephrine effects the conducting mechanism received adequate blood since its demand for blood was affected but little.

These conclusions are supported by the accentuation of the epinephrine effect following section of the vagi. The removal of this inhibiting mechanism leads to further increase in myocardial activity and therefore greater oxygen need.

## SUMMARY

Electrocardiographic studies were made after the injection of epinephrine into the saphenous vein and the coronary artery and following vagotomy. The electrocardiographic changes caused by epinephrine are ascribed to its increasing the myocardial requirements for oxygen beyond the available supply, thus resulting in functional anoxemia of the myocardium.

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# PRODUCTION BY EPINEPHRINE OF S-T CHANGES IN THE ELECTROCARDIOGRAM OF THE CAT, SIMILAR TO THOSE OF CORONARY OCCLUSION*

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SIR THOMAS LEWIS, in collaboration with B. Gelfand, showed in 1935 that the thrombosis produced by ergot in the cock's comb was secondary to arterial spasm.[1] This work suggested the possibility that coronary artery thrombosis in man might, at times, be precipitated by spasm of these arteries. In order to throw some light on this problem we were interested in the possibility of producing thrombosis in the coronary arteries of the cat by the use of drugs that cause arterial spasm. Among the drugs used was epinephrine. We were impressed with the ability of epinephrine in suitable doses to produce in the electrocardiogram of the intact, unanesthetized cat S-T displacement similar to that seen in the most extreme changes of coronary occlusion. We are reporting these changes in this paper. They provide confirmatory evidence of the ability of epinephrine to produce spasm of the coronary arteries and seem to offer a simple test of the ability of various drugs to cause dilatation of these arteries.

## METHOD

From 1.5 to 2 c.c. of epinephrine 1:1000 (Armour) was injected into the thigh muscles of intact, unanesthetized cats. Control electrocardiograms were taken prior to treatment. Frequent electrocardiograms were taken after the administration of the epinephrine and, after marked S-T changes were produced, nitroglycerin gr. $\frac{1}{50}$, in aqueous solution, was injected into the opposite thigh muscle and further electrocardiographic studies made. Seventeen experiments were done, using eight cats.

In the normal electrocardiogram of the cat Lead I usually shows deflections that are almost isoelectric, and Leads II and III are very similar in appearance. For this reason transient changes were followed in Lead II, although all three leads were taken whenever time permitted.

Cambridge electrode jelly was used and lead electrodes were applied directly to the skin. The string was standardized to deflect 1.5 cm. to a millivolt.

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## RESULTS

Marked S-T displacement was obtained in all experiments and in many this displacement was so marked that the QRST curve was monophasic in type. In most experiments the S-T interval was depressed below the isoelectric line, but in some the change took place in the opposite direction. Two typical experiments are outlined below, one illustrating the production of marked S-T elevation and the other showing marked S-T depression.

Experiment No. 4, Nov. 2, 1936. Control electrocardiogram normal. One and one-half cubic centimeters of epinephrine 1:1000 was injected into the right

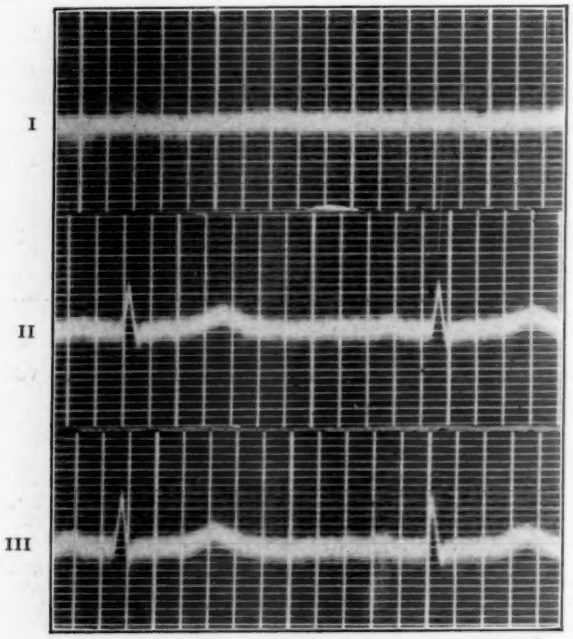


Fig. 1.—Experiment 4. November 2, 1936. Control electrocardiogram, Leads I, II, and III.

thigh muscles. An electrocardiogram taken at once showed slowing of the rate and then the production of a nodal rhythm. Five minutes after the administration of the epinephrine marked elevation of the S-T interval was found in all three standard leads, and in six minutes a monophasic curve was obtained (Figs. 1, 2, and 3). There was a rapid return of the displaced S-T segment toward the isoelectric line and in twelve minutes the segment was again isoelectric.

On Nov. 6, 1936, the same experiment was repeated with the same animal. Again marked elevation of the S-T interval was produced in five minutes, although not as marked as in the first experiment on this animal. The change persisted for twenty minutes.

On Nov. 13, 1936, the experiment was repeated a third time with the same animal. This time no S-T displacement was obtained.

Experiment No. 9, Dec. 5, 1936. Control electrocardiogram normal. One and one-half cubic centimeters of epinephrine 1:1000 was injected into the right thigh muscles. A tracing taken two minutes after the injection showed marked slowing. In five minutes S-T depression appeared and tracings taken at nine and nine and one-half minutes showed very marked depression of the S-T segment (Figs. 4, 5, and 6). At the ten-minute mark nitroglycerin, gr. 1/50, was injected into the left thigh

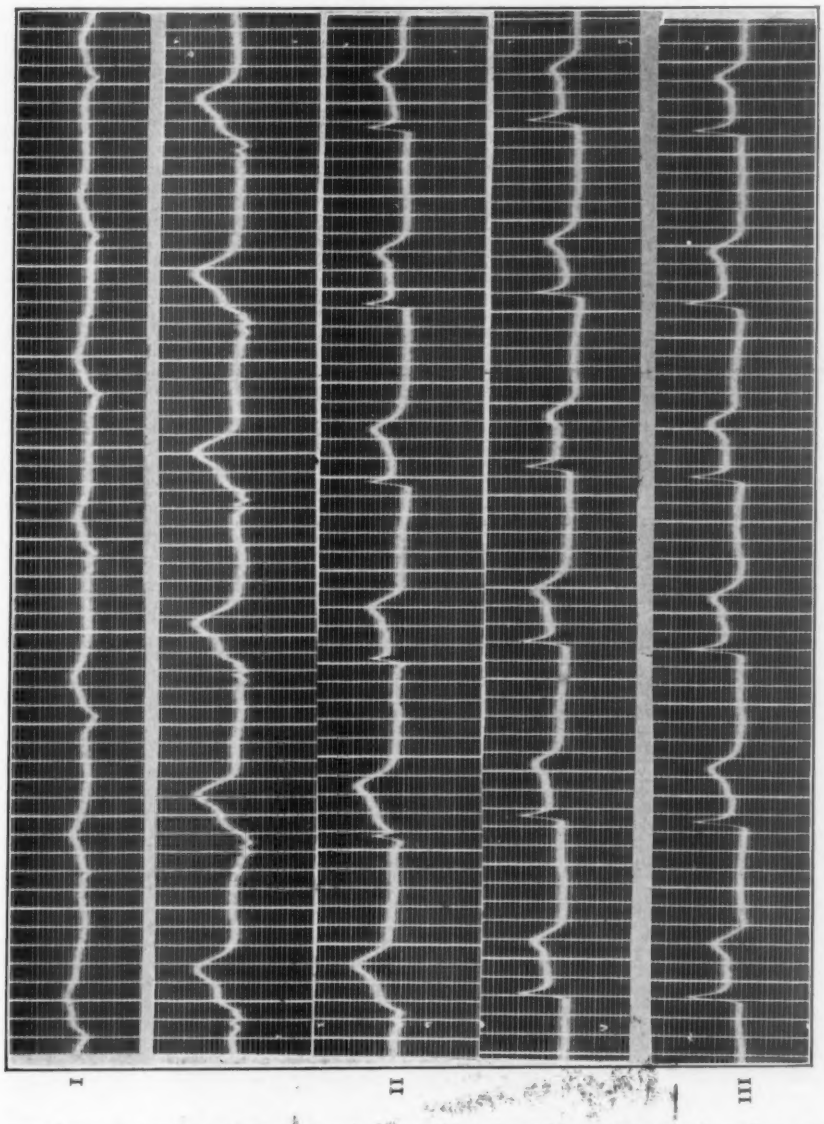


Fig. 2.—Experiment 4. Six minutes after injection of epinephrine. Lead I, Lead II—continuous strips—and Lead III.

muscles. A tracing taken as soon as possible after this treatment showed return of S-T to the isoelectric level, and the T-wave, which had been inverted, became upright. The effect of the nitroglycerin was very transient. One minute after its administration there was a return to a depressed S-T interval and an inverted T-wave and this type of curve continued for three and one-half minutes after which the S-T interval was isoelectric, although the inversion of T lasted for about twenty-five minutes.

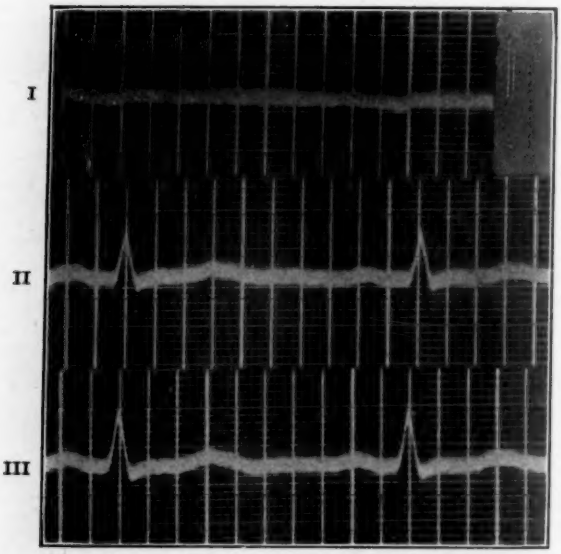


Fig. 3.—Experiment 4. Twenty-five minutes after injection of epinephrine showing return to normal, Leads I, II, and III.

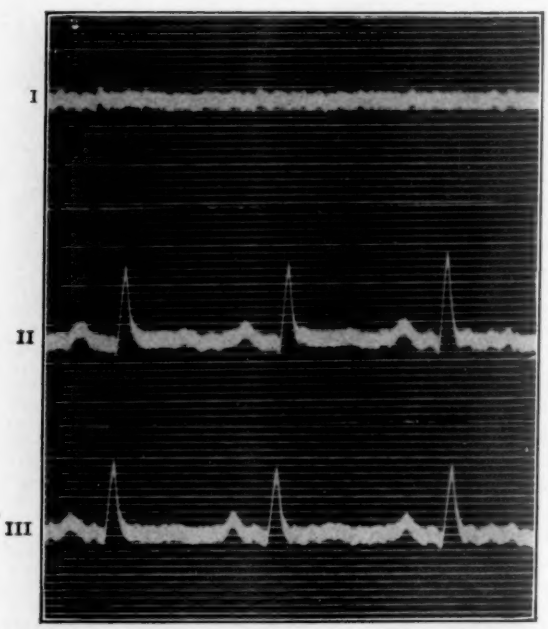


Fig. 4.—Experiment 9. Dec. 5, 1936. Control electrocardiogram, Leads I, II, and III.

## DISCUSSION

In 1920, Pardee[2] called attention to the S-T displacement in the electrocardiogram with acute coronary occlusion in man. Much experimental work has appeared since in which similar changes were produced in

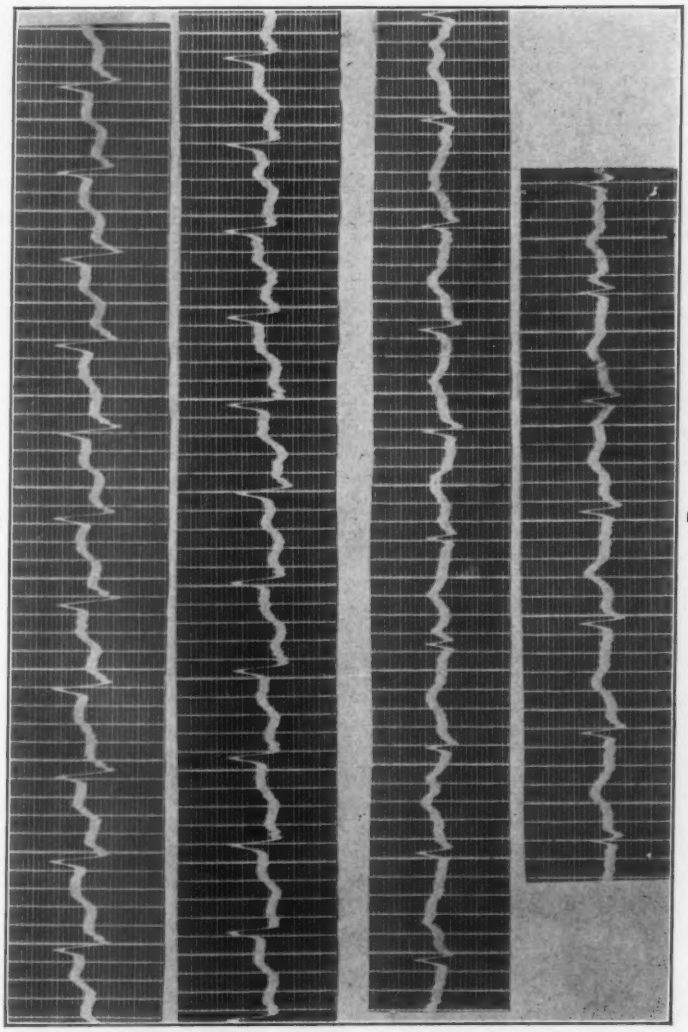


FIG. 5.—Experiment 9. *A*, Nine and one-half minutes after injection of epinephrine, Leads II and III; *B*, immediately after injection of nitroglycerin, about 10¾ minutes after epinephrine, Leads II and III.

animals. In most of this experimental work the heart was exposed and subjected to various mechanical, chemical, thermal, and electrical procedures.[3] In other experiments the same type of electrocardiographic curve was produced in the intact animal by anoxemia,[4-7] insulin,[8] digitalis,[9] and pitressin.[10] We show in this paper that epinephrine in suitable doses can produce similar changes; that these changes are consistently produced, unlike those caused by digitalis or insulin; and that

they are as marked as the changes reported by Kountz and Gruber[10] with pitressin in anoxemic dogs. As in the latter work the changes could be made to disappear by the administration of nitrites.

As Fig. 2 and 5 illustrate, the displacement of S-T produced by epinephrine can be above or below the isoelectric level, and can be marked

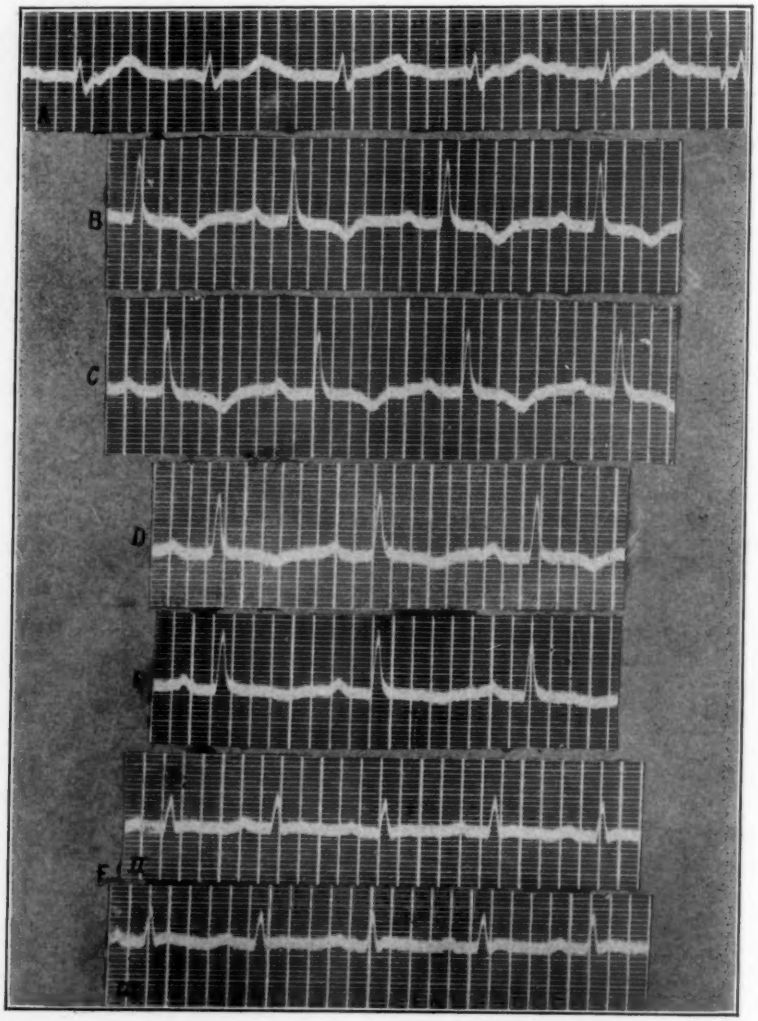


Fig. 6.—Experiment 9. *A*, Lead II taken one-half minute after injection of nitroglycerin; *B*, one minute later; *C*, two minutes after; *D*, ten minutes after; *E*, twenty-five minutes after; *F*, Leads II and III one hour after the injection of nitroglycerin.

enough to make the QRST curve monophasic. The fact that nitroglycerin can cause a quick but transient return to normal suggests that the changes are the result of spasm of the coronary arteries, probably secondary to stimulation of the sympathetic nerve endings that supply these vessels. In some experiments paroxysmal ventricular tachycardia

induced by epinephrine was quickly abolished by nitroglycerin. This suggests that coronary artery spasm is not only responsible for the S-T segment change but also plays a part in the initiation of arrhythmias.

The electrocardiographic effects of epinephrine in animals have been studied by a number of authors.[12, 13] These authors, however, used smaller doses than those injected in our experiments and emphasized disturbances in cardiac rate and rhythm. When S-T displacement was produced it was much less marked than the changes reported in this paper. In the present study we have been interested primarily in the action of epinephrine on the S-T segment and the coronary arteries. That the drug has, in addition, a direct action on the sympathetic nerve endings in the heart apart from the coronary arteries, and an indirect, reflex action from the hypertension it causes, has been demonstrated by others.[11, 12]

The effect of epinephrine on the electrocardiogram has been studied in man as well as in animals. Anginal seizures and S-T displacement have been produced[7, 14-16] but the S-T changes were slight, probably because the doses used were necessarily small.

In addition to electrocardiographic studies many direct investigations have been made of the action of epinephrine on the coronary arteries and the coronary circulation. The earlier work has been reviewed by Gruber and Roberts.[17] These authors worked on the perfused, excised hearts of cats, rabbits, and rats and concluded that the drug in dilute solutions causes vasodilatation, and in concentrated solutions, vasoconstriction. Our findings are consistent with these conclusions and add further evidence to support the view that epinephrine can cause marked coronary artery spasm.

We believe that the S-T displacement caused by epinephrine in the electrocardiogram of the cat might be used as the basis for a simple test of the ability of other drugs—e.g., theobromine or theophylline—to relieve coronary artery spasm. The changes are conspicuous, and can be consistently and easily produced.

## CONCLUSIONS

1. Epinephrine in suitable doses can produce marked displacement of the S-T segment of the electrocardiogram of the cat. This displacement can be above or below the isoelectric level. It can be so marked that a monophasic curve results.

2. The S-T changes produced by epinephrine can be abolished by nitroglycerin.

3. These changes are probably the result of coronary artery spasm.

4. They can be used as a basis for testing the ability of drugs to relieve coronary artery spasm.

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# ANOMALOUS ORIGIN AND COURSE OF THE LEFT CORONARY ARTERY IN A CHILD

## So-called Congenital Absence of the Left Coronary Artery*

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THE type of anomaly here reported usually appears in the literature under the title of congenital absence of the left or right coronary artery. All authors recognize the fact, however, that the essential lesion consists not of an absence of the vascular supply, ordinarily provided by the coronary artery in question, but of an abnormality of its origin, course, and distribution.

Upon examination, the reputedly absent coronary artery cannot be found running from the aorta in normal position; its orifice is completely lacking. In one group of cases the artery arises—either in itself or in its branches—along with or from the homologous coronary vessel. In a second group anatomical counterparts of the absent artery are not distinguishable as such. Then the coronary artery which is considered to be present gives off branches and terminations that act as functional substitutes. Because of the anomalies in origin, the components of the coronary circulation also assume variations in caliber and course.

### REVIEW OF LITERATURE

References to the anomalous origin and course of the coronary artery here presented, as an isolated cardiac defect are rather few. Mention is made of it in the classical literature by Galen, Bartholinus, Fantonus, Morgagni, and Thebesius. In their works Otto, Cruveilhier, Gegenbauer, Kaufmann, Maude Abbott,[1] and Bland, White and Garland[2] offer brief citations. During the past one hundred years complete descriptions of only eleven cases have appeared in the medical journals; two of these are recorded in the American literature.

In Hyrtl's case[3] (1841) the subject was a seven-month fetus. The right coronary artery was missing; it was replaced by branches from the left coronary artery.

In Buchdalek's case[4] (1867) the patient was a sixty-year old woman. The cause of death was not given. The left coronary artery was anomalous. A single artery sprang from the right sinus of Valsalva and soon divided into three branches. One of these corresponded to the normal right coronary artery. The second passed between the aortic root and left auricle and took the place of the left circumflex branch. The third branch traversed a path to the left, through the

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muscle of the posterior wall of the left ventricle and interventricular septum, and came out on the surface as the left anterior descending artery. Histological sections were not described.

In Engelman's case[5] (1898) the age and the sex of the patient and the cause of death were not tabulated. The right coronary artery was abnormal. A single artery originated behind the left anterior cusp. It broke shortly into a vertical and horizontal branch. The former ran anteriorly and gave off a small branch which passed to the right between the pulmonary artery and the aorta to the posterior surface of the heart and an abnormally large branch to the anterior wall, margo acutus, and the posterior wall of the right ventricle. The horizontal branch followed the course of the left circumflex vessel. Histological descriptions were not included.

In Plaut's case[6] (1922) the patient was a thirty-seven-year-old man. He suffered primarily from subacute bacterial endocarditis. The right coronary artery was called absent. In the right sinus of Valsalva only a small dimple could be seen. The left coronary arose at the normal site. The circumflex branch ran in the sulcus atrioventricularis of the whole heart and ended in a small branch 3 cm. from the usual origin of the right coronary artery. Along its course this artery gave off three branches to the left, and three small branches to the right anterior cavity, and numerous branches to the posterior surface of the heart. Twelve centimeters from the origin of the left anterior descending artery, a large branch proceeded down to the right to both surfaces of the right heart. The anomaly was not connected with the cause of death. Histological descriptions were not given.

In the case of Gallavardin and Ravault[7] (1925) the patient was a forty-five-year-old woman who was afflicted with chronic mitral and aortic endocarditis. The left coronary artery was anomalous. The aorta presented one coronary orifice in the right sinus. From a small common trunk passed a normal right coronary artery and a second vessel which sank into the ventricle between the pulmonary conus and the right auricle to emerge and to divide into a left descending and a circumflex branch. The last was not entirely normal and formed two branches. The anomaly did not figure in the death of the patient. Histological sections of the myocardium were not described.

In the case of Smith and Graber[8] (1926) the patient was a forty-six-year-old man. Death was caused by coronary thrombosis. The left coronary artery was called absent. There was only one coronary orifice in the right anterior sinus. The artery leading from this opening was large and followed the usual course of the right coronary artery. Posteriorly it divided into two branches. The larger descended along the interventricular septum, where it was found thrombosed. The smaller continued around the atrioventricular groove to the margin and the apex of the left heart to pass upward on the anterior

surface. Here it joined a large artery coming down over the base of the right ventricle from the first portion of the main coronary artery, which continued to the posterolateral aspect of the left ventricle. The thrombotic lesion in the anomalous coronary circulation produced death. Microscopically the myocardium showed fibrosis.

In Gratzer's case[9] (1926) the patient was a sixty-eight-year-old woman. She died from thrombophlebitis of the veins of the legs, and pulmonary infarcts. The heart showed myomalacia, parietal thrombosis, and aneurysm of the wall. The left coronary was anomalous. Three orifices were seen in the right sinus of Valsalva. The middle opening gave off the largest vessel, which traveled through the right atrioventricular sulcus to the posterior wall of the right ventricle, distributed a branch to the posterior sulcus and continued to the left heart. From the left ostium there arose a vessel which supplied the anterior part of the left ventricle and the apex. From the right ostium a vessel was traced to the right anterior heart. The anomaly apparently did not figure in the cause of death. Histological sections were not described.

In Petren's case[10] (1930) the patient was a thirty-three-year-old man. Death was attributed to hypertension and cerebral hemorrhage. The right coronary artery was abnormal. The left coronary artery arose from a large opening and divided into anterior and circumflex branches. At the apex the anterior descending artery turned to the right ventricle. The circumflex branch crossed posteriorly and gave off descending branches to the left ventricle, the posterior sulcus, and the right ventricle. Death was not connected with the anomalous vessel. Histological descriptions were not included.

In Kintner's case[11] (1931) the patient was a sixty-five-year-old man. Death was caused by renal insufficiency and pulmonary embolism. The left coronary artery was anomalous. The right coronary orifice was larger than normal and served as a common opening for two vessels. The larger of these went through the right coronary sulcus to the posterior heart. A small artery passed from the common orifice down to the left at the root of the aorta beneath the muscle of the posterior wall, then through the interventricular septum. It finally reached the anterior surface of heart and divided into left ascending and descending arteries. The former replaced the left circumflex branch; the latter, the left anterior descending branch. The anomaly played no part in the cause of death. Histological descriptions were not given.

In Born's case[12] (1933) the patient was a fifty-four-year-old man. The primary cause of death was empyema and pulmonary gangrene. The left coronary artery was absent. From a common opening issued the left and right coronary arteries. The first ran between the aorta and the conus pulmonalis into the septum and emerged to give off the left descending and circumflex branches. The right coronary artery helped supply the left ventricle posteriorly. Death was not associated with the anomaly. Sections were not described.

In Kockel's case[13] (1934) the patient was a thirty-nine-year-old woman. She died of pneumonia and pericarditis. The right coronary artery was anomalous. The left coronary artery divided into left anterior descending and left circumflex vessels. These provided branches to anterior and posterior parts of the right heart. The anomaly played no part in the cause of death. No histological description was given.*

## REPORT OF CASE

*History.*—J. B., a white American male child, aged three years and ten months, was admitted to the Buffalo Children's Hospital on Aug. 21, 1936, because of generalized edema of several days' duration. He died within two days.

The father and mother, each 33 years of age, were in good health. The patient was the last of five children. He was born at full term. Delivery was spontaneous and uneventful. At birth the child did not emit a cry but seemed to breathe normally. There was no cyanosis. Immediately after birth bilateral strabismus was noted. Our patient was breast fed for nine months. He had received no cod liver oil or orange juice. He had never talked or walked, though he climbed nimbly. Immunization for diphtheria had been carried out. Except for occasional colds, the past history was negative.

Several days before hospital entry, the patient became listless. Edema was noted by the mother. The urine was scanty and highly colored.

*Examination.*—The temperature was 100° F.; pulse, 120; and respiratory rate, 28. The weight was 27 pounds. The child was well developed and well nourished but pale. He showed generalized pitting edema. The biparietal diameter of the skull was narrow; the fronto-occipital diameter, long. Bilateral internal strabismus was present. Pinpoint hemorrhages were noted in the fundi. Both nares contained dried blood. The tonsils were large. The lungs were apparently clear. The heart was not enlarged. The blood pressure was 70 systolic and 30 diastolic. The right testicle was undescended. Deep reflexes were hypoactive. Examination of the urine was negative. The clinical impression was acute glomerulonephritis and chronic tonsillitis.

## AUTOPSY FINDINGS

The autopsy was made eight hours after death. The final diagnosis comprised acute diffuse glomerulonephritis; marked edema and congestion of both lungs, with patchy areas of atelectasis of the lower lobes; slight bilateral hydrothorax; slight hydropericardium; slight ascites; edema of the soft tissues; diffuse myocarditis; acute interstitial hepatitis; recent interstitial myositis (diaphragm); acute splenitis; congestion of the brain; anomalous origin and course of the left coronary artery; anomalous course of the right coronary artery; synostosis of the skull; bilateral strabismus. The line of ossification was regular. No lesions were found in the stomach or the intestines. Peripheral nerves were examined.

*Description of the Heart.*—On removal of the sternum, the pericardium was found slightly distended. The pericardial fluid was straw colored and slightly increased in amount. The longitudinal diameter of the heart measured 7 cm.; the horizontal diameter at the atrioventricular sulcus, 7 cm. The weight was 60 gm. The apex was somewhat rounded. The epicardial fat was normal in amount. The vessels on the surface of the heart were very prominent and tortuous.

The aortic cusps were three in number. They showed no vegetation. That of the right anterior sinus was slightly fenestrated. No coronary orifice was seen in the

*In a forty-year-old woman who died from malignant hemangioma, Hall[14] noted that the right coronary artery had no opening into the aorta but that the artery was found in epicardial fat about 1 cm. from the aorta.

left anterior sinus. A shallow dimple—pinhead sized—was present in the anterior sinus close to the commissure between both anterior sinuses. This dimple was not in the position of the normal origin of the left coronary artery. In the right sinus of Valsalva was situated a large orifice 0.25 cm. in diameter. When it was stretched, the large orifice revealed three moderate-sized openings and one very minute

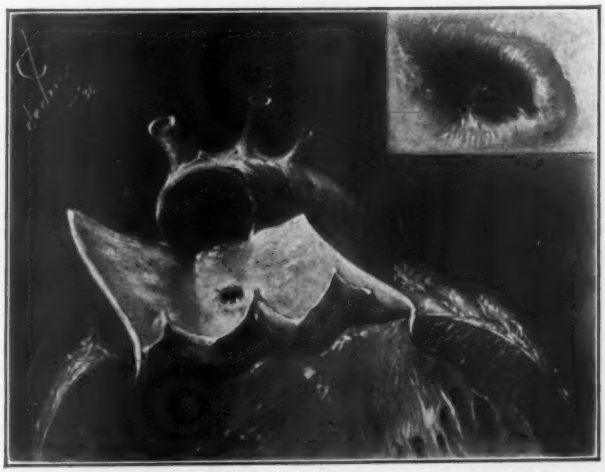

Fig. 1.—Gross view of aorta showing common coronary orifice in right anterior sinus. Inset depicts magnified common orifice and adjacent minute opening.


Fig. 2.—Diagram of course and distribution of coronary arteries. *A*, left descending branch passing through the interventricular septum. Stippling indicates continuation of arteries on the posterior surface of the heart.

opening. The moderate sized openings were arranged so that two occupied a superior position, and one a site midinferior to the upper two. The minute opening lay between the right superior and midinferior orifices. An additional minute opening was noted in right sinus just medial to large orifice. From the right superior opening emerged a vessel which corresponded to the right coronary artery. It measured 0.3 cm. in circumference. Three large branches to the right anterior

ventricle, a large branch to the margo acutus, and small branches to the right atrium were given off. Traveling in the atrioventricular sulcus, the vessel, interpreted as the right coronary artery, continued beyond the margo acutus to the posterior part of right ventricle. Here it distributed a large branch to the posterior descending sulcus. The vessel was next traced (still in the atrioventricular sulcus) for a distance of 2 cm. on to the posterior wall of the left ventricle. A large branch passed downward and diagonally to margo obtusus, and thence to the anteroinferior part of the left ventricle. The main right coronary artery was followed another centimeter in atrioventricular sulcus; it terminated at margo obtusus. The right coronary artery measured 10 cm. in length.

The left superior opening in the right anterior sinus gave origin to a vessel that sank into septum between pulmonary artery and aorta and penetrated downward for a distance of 1 cm. At this point it made a 125-degree-angle turn toward the anterior surface of the heart. After 1 cm. the artery reached the subepicardium at the interventricular sulcus 2.2 cm. from the aortic ring. On the surface of the heart, it conformed to the topography of the left anterior descending branch for 3 cm. and supplied both the left and the right ventricles.

From the midinferior opening a vessel passed behind the posterior and left aortic cusps to the left. It came out in the left interventricular sulcus at junction of anterior mitral leaflet and the left aortic cusp. This artery was 4 cm. in length and corresponded in part to the left circumflex branch. It gave off small branches to the anterior part of the left ventricle and the margo obtusus.

The two minute openings in the right anterior sinus could not be probed or dissected because of their size. The veins of the heart were not remarkable. The superior and inferior venae cavae were not remarkable.

The right auricular appendage contained no thrombi. The wall of the right atrium measured 0.08 cm. The tricuspid valve was thin and delicate. It measured 6.5 cm. in circumference. The wall of right ventricle was 0.3 cm. thick. The cavity measured 5.8 cm. The chordae tendineae and the papillary muscles were not remarkable. The pulmonary artery was free. It measured 4 cm. above the valve. Pulmonic cusps showed slight fenestration. The pulmonary veins were patent. The foramen ovale was closed. The left auricular appendage was clear. The endocardium of the posterior wall of the right atrium showed few white ridges. The wall measured 0.18 cm. The mitral valve was 5 cm. in circumference. The anterior leaflet showed an atheromatous patch 0.2 cm. in diameter. The wall of left ventricle measured 0.5 cm.; the cavity, 5 cm. The aorta measured 3 cm. above the valve.

On section the color of the myocardium of the left ventricle especially of its posterior wall was pale. Scattered throughout were small gray patches and streaks. Dilated vessels and petechial hemorrhages were also seen.

*Microscopic Findings.*—Blocks of tissue were taken from various parts of ventricles and atria and fixed in 10 per cent formaldehyde. Frozen and paraffin sections were made and stained with hematoxylin-eosin, van Gieson, Weigert elastic, Gram-Weigert, sudan III, methyl green-pyronine, and Levaditi methods. Studies of the sections revealed that changes were present in both ventricles. The findings were most marked in the left ventricle and in the posterior wall of the left ventricle. The histological picture included a distinct recent diffuse interstitial myocarditis, parenchymatous degeneration and atrophy of myocardial fibers, dilatation of capillaries, recent interstitial hemorrhages, and epicarditis.

The lesion in the left ventricle will be described. The endocardium was normal in thickness. Fibrosis and elastification could not be made out. No thrombi were seen on the surface. Throughout the wall distinctly atrophic fibers could be distinguished between those of normal size.

At first glance the three myocardial zones appeared to take the hematoxylin-eosin stain evenly. However, upon tracing the course of individual fibers, one noted

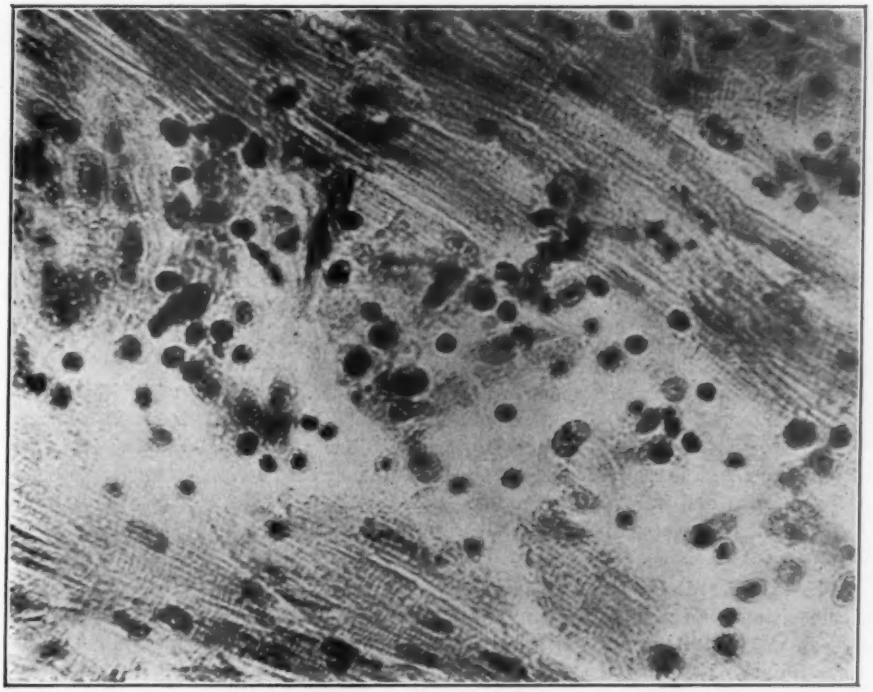

Fig. 3.—Section of myocardium showing interstitial edema and cellular infiltration.

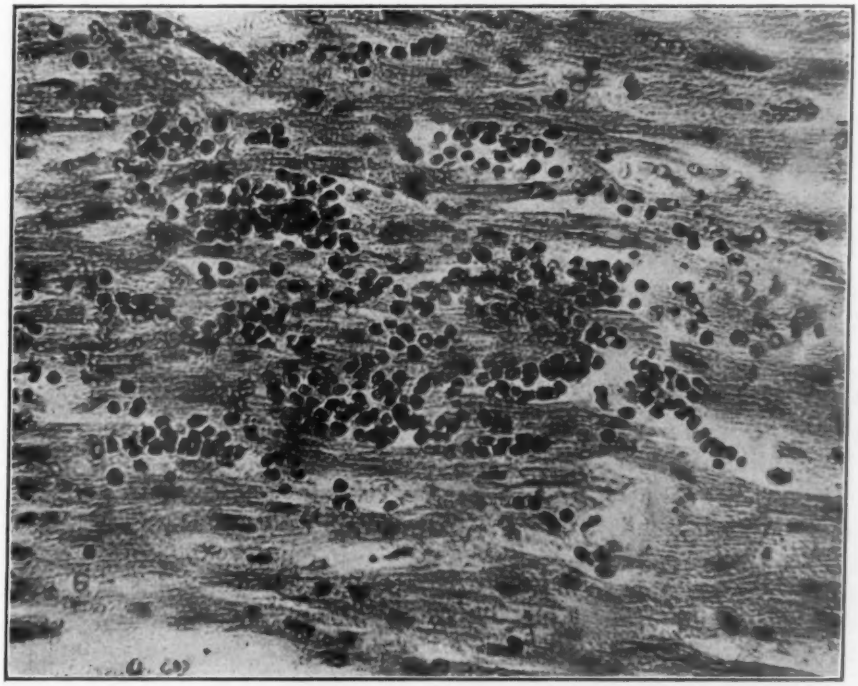

Fig. 4.—Section of myocardium showing injected capillaries and recent interstitial hemorrhages.

that areas which took a pale stain were scattered along intensely pink-staining fibers. Under high power the pale areas showed loss of striations and frayed fibrillae. In the outer zone of myocardium vacuoles were present in sarcoplasm. Nuclei were pale—oval or rectangular in shape; chromatin material was not prominent. In some pale areas the muscle fibers had disappeared with formation of gaps. In others the sarcolemma alone was preserved. Sudan stain revealed fatty degeneration in patchy distribution.

The most striking variations from normal in the myocardium were observed not in the muscle fibers themselves, but in interstitial spaces and in the gaps mentioned above. Muscle fibers were separated by edema. Capillaries were dilated. In the interstitial spaces and gaps were neutrophiles, eosinophiles, round cells, mast cells, and plasma cells. There were marked proliferations of fixed tissue cells. These appeared as oval cells with vesicular nuclei. Few macrophages had indented or double nuclei. The cellular infiltration was found in all zones. The areas of infiltration in different sections ran parallel to muscle fibers and in perpendicular zigzag courses. With the van Gieson stain thin collagenous fibrillae were noted running in interstitial spaces. The perivascular tissue about the moderate sized coronary arteries showed edema and infiltration of neutrophiles and plasma cells, and proliferation of histiocytes. Often around the vessels there was a halo of edema. No distinct nodular arrangement was seen. The branches of the coronary arteries were patent.

The subepicardial tissue showed cellular infiltration and histiocytic proliferation. These changes reached in between the muscle fibers of the outer muscle zone. In certain sections recent interstitial hemorrhage had occurred in the myocardium. The endocardium of the mitral and the aortic valves was not remarkable. Bacteria were not found.

## DISCUSSION

Discussion of the case just described will be concerned for the most part with two questions. In what respects does our case contribute to the knowledge of anomalous origin and course (so-called congenital absence) of either coronary artery? What explanations have been proffered for occurrence of the anomaly?

In our case the coronary arteries arise in the right anterior aortic sinus from a common orifice which houses three moderate sized openings and one minute opening, and from one separate minute opening. This type of origin is not duplicated among the eleven reported examples of anomalous left or right coronary artery.

The distribution of branches of the coronary arteries in our case, however, corresponds to the findings of other authors in certain cases of anomalous coronary artery. In fact, these cases, by a characteristic distribution of vessels, form a distinct group—that of anomalous left artery. In this group the left anterior descending branch arises separately or from right coronary artery, penetrates the interventricular septum, and emerges on the anterior wall of left ventricle. The left circumflex branch passes between the aortic root and the left auricle to reach the atrioventricular sulcus. In a second group of anomalous left coronary artery, the left circumflex branch is absent or rudimentary. In both groups the right coronary artery gives off branches to the left ventricle.

Reported cases of anomalous right coronary artery also follow a uniform vascular distribution. The left artery divides into a left anterior descending and a circumflex branch. These supply vessels to anterior and posterior parts of right heart.

Cognizance of the classification of anomalous coronary artery on the basis of vascular distribution, which is formulated here for the first time, ought to preclude further arguments on the nosological question: Is it proper to term the anomalous artery absent or not? In the anomalous left coronary artery, exemplified by our case, the abnormal vessel—from a strict anatomicophysiological sense—cannot be said to be absent. The developmental defect lies in an absence of its orifice at the customary site in the aorta and in the abnormality of its branches and course. Branches corresponding to those of the ordinary left coronary artery are present; in addition, branches from the right coronary artery supply the left ventricle.

On the other hand, cases of anomalous right coronary artery, from an anatomical point of view, may be justifiably called instances of congenital absence of the right coronary artery. Counterparts of branches of the right coronary artery are not manifest.

Our case is the first instance of so-called congenital absence of the coronary artery to be discovered in a child. This fact is important because in a child's heart we are able to study the possible effects of the anomalous coronary artery on the myocardium without having to take into account cardiac lesions of adult life, such as coronary arteriosclerosis.

Histological description of the myocardium occurs in but one recorded case of anomalous origin and course of the coronary artery (Smith and Graber). Here, any causative relation of the anomalous coronary artery is hard to evaluate, for the microscopic changes can be explained by a coronary thrombosis; the effects of the anomalous vessel, if present at all, are completely overshadowed by the superimposed vascular obturation.

In our case distinct histopathological findings are noted in the myocardium. Indeed, these could already be detected grossly. The myocardial damage consists chiefly of a recent diffuse myocarditis, interstitial and parenchymatous in type, capillary dilatation, and recent hemorrhages. The problem of the etiology and pathogenesis of this damage must be faced. Are the lesions due to an alteration in blood supply brought about by the anomaly? Or are they dependent on an unrelated etiological factor? Is the combination of such a factor with the coronary anomaly merely a coincidence? Or may the anomaly predispose the myocardium to the deleterious action of another pathogenic agent?

Claims have been made that the portions of the heart supplied by the anomalous coronary artery receive a diminished circulation. Physiological substantiation for this belief has never appeared. It is

true, however, that the branches of the anomalous vessel are not of usual length; their caliber tends to be small. Though the artery which is considered to be present assumes added function, it does this through secondary or end branches. None of the hearts in the literature has been studied radiographically for the extent of anastomoses. But in infants and children coronary anastomoses are normally least developed; the left ventricle possesses normally a lesser blood supply than the right. Yet, to our mind the explanation for the myocardial changes in our case solely on the assumption of diminished blood supply and diminished oxygen supply attendant upon the anomaly, is not completely satisfying. The myocardial changes are recent; the inflammatory lesion is most prominent; scarring as from coronary insufficiency, either mechanical or functional in origin, is not seen.

In a search for primary etiological and pathogenic factors besides the coronary anomaly, we can rule out syphilis, severe anemia, myxedema, embolism, von Gierke's disease, rheumatic fever, beriberi, and bacterial myocarditis. Toxic or infectious-toxic myocarditis must be considered first. Interstitial myocarditis has been described in uremia. Our patient died from acute glomerulonephritis. Blood chemistry determinations for urea nitrogen were not carried out *intra vitam*. On an infectious-toxic basis, the cardiac lesion could fit in with changes in kidney, liver, muscle, and spleen.

It is difficult to say how far the effects, if any, of the anomalous coronary artery increased the susceptibility of the myocardium to the action of some toxin. We must note that the left ventricle and its posterior wall, which would suffer the consequences of the anomalous blood supply, are apparently most involved in the myocardial lesion. (But myocarditis can attack one side of the heart to a greater degree than the other.) Muscle fibers show atrophy and fatty degeneration. When we realize, however, that ours is the first case of so-called congenital absence of coronary artery reported with adequate histological studies, we believe it is safest to record our findings without drawing categorical conclusions. Microscopic descriptions in future cases may help to decide whether the anomalous coronary artery produces any primary or predisposing effects and whether the myocardial damage in our case is only an accident.

Plaut[6] sought an explanation for the "absence" of the coronary artery on embryological and phylogenetic grounds. Embryology offered little clarification. The first anlage of the coronary arteries in the rabbit appears as a thickening in the aortic endothelium from the twelfth to fourteenth days of embryonic life and just before truncus arteriosus has been divided into aorta and pulmonary artery. The left coronary artery is formed first. In the beginning the arterial rudiments are solid columns of cells which later acquire a lumen and grow outward into the superficial portion of the myocardium.[2]

In comparative anatomy Plaut found an interesting implication. In fish and amphibia there is only one coronary artery. In chelonidiae and sauridiae the number is often reduced to one or increased to three. Only 60 per cent of the birds have two vessels. Mammals as a rule show two coronary arteries. The development of two coronary arteries seems to be a late acquisition in the evolutionary process, associated with separation of heart chambers.

Before the diagnosis of so-called congenital absence of the coronary artery is ventured, origin from the pulmonary artery or from a position high in the aorta must be looked for. Complete occlusion of one coronary orifice by syphilis or arteriosclerosis should be excluded. So-called congenital absence of the coronary artery is sometimes associated with other major cardiac anomalies.[15]

## SUMMARY

The literature on so-called congenital absence of coronary artery as an isolated anomaly is reviewed. A case which illustrates this anomaly of the left coronary artery in a four-year-old boy is reported. Findings of unique significance include the type of origin of coronary arteries, the age of the patient, and the pathological changes in the myocardium.

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# APPARENT INCREASED VELOCITY OF BLOOD FLOW IN CASES OF CONGENITAL HEART DISEASE WITH SEPTAL DEFECTS HAVING RIGHT-TO-LEFT SHUNT*

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WHILE engaged in a study of the hemodynamics of morbus caeruleus we noted an extreme "acceleration" of blood flow in a patient exhibiting the clinical syndrome associated with tetralogy of Fallot (patent interventricular septal defect, right ventricular hypertrophy, pulmonary stenosis, and dextroposition of the aorta). It occurred to us that this remarkable "acceleration" in velocity was apparent rather than real and was dependent upon a "short circuiting" through the patent interventricular septum. It is obvious that if this be correct a simple diagnostic test for septal defects with right-to-left shunt would be available.

The arm-to-carotid sinus circulation time was measured by the sodium cyanide method of Robb and Weiss.[1] This simple test consists of the rapid injecting of a 2 per cent solution of sodium cyanide into an antecubital vein and observing the time of the appearance of a sudden deep inspiration. The amount of cyanide given is determined on the basis of 0.11 mg. for each kg. of body weight. The test ordinarily measures the time necessary for blood to pass from the antecubital vein, through the right heart to the lungs, plus the time of passage through the lungs and the left heart to the carotid sinus. Robb and Weiss have shown that in the healthy adults the average arm-to-carotid circulation time is 15.1 seconds, the maximum time being 20 seconds, the minimum, 10 seconds. Likewise they showed that the time necessary for the cyanide to pass from the antecubital vein to the lung in normal adults (the venous velocity) averaged 4.5 seconds, while the crude pulmonary circulation time was 10.6 seconds.

The reaction taken as the end point in children was very definite and clear cut. The optimal reactive dose was found to be 0.13 mg./kg. for children as contrasted to the value of 0.11 mg./kg. obtained by Robb and Weiss for normal adults.

As no reported studies in children have been made with the cyanide method we have examined 11 normal children and found that the circulation time is shorter than in adults, averaging 10.6 seconds (Table I), maximum being 14.5 and minimum 9.0; in one child showing marked excitement and apprehension, a circulation time of seven seconds was

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TABLE I

CONTROL CHILDREN—ARM-TO-CAROTID SINUS CIRCULATION TIME WITH NaCN

| NAME | AGE | SEX | WEIGHT (LB.) TEMPERATURE (° F.) | AMOUNT OF NaCN (2% SOLUTION) INJECTED | CIRCULATION TIME (SECONDS) | PULSE BEFORE | PULSE AFTER | B. P. | INTENSITY OF REACTION |
|---|---|---|---|---|---|---|---|---|---|
| A. S. | 10 | F | 50 lb.<br>T. 98.2 | 0.17 c.c.-0.15 mg./kg. | 9.0 | 118 | 122 | 85/65 | + |
| M. F. | 10 | M | 62<br>T. 98.0 | 0.20 c.c.-0.14 mg./kg. | 11.2 | 110 | 102 | 105/60 | + |
| H. D. | 12 | M | 85<br>T. 98.4 | 0.25 c.c.-0.13 mg./kg. | 13.5 | 100 | 85 | 100/70 | + |
| C. P. | 7 | M | 35<br>T. 99.0 | 0.16 c.c.-0.18 mg./kg. | 10.8 | 114 | 100 | 90/60 | ++ |
| A. C. | 11 | M | 56<br>T. 98.0 | 0.17 c.c.-0.13 mg./kg. | 11.5 | 88 | 74 | 95/65 | ++ |
| N. M. | 8 | M | 38<br>T. 98.0 | 0.15 c.c.-0.17 mg./kg. | 10.0 | 80 | 78 | 105/70 | + |
| S. C. | 10 | M | 65<br>T. 98.0 | 0.17 c.c.-0.11 mg./kg. | 9.0 | 120 | 114 | 110/50 | ++ |
| S. K. | 7 | F | 50<br>T. 97.8 | 0.17 c.c.-0.11 mg./kg. | 9.0 | 78 | 90 | 95/60 | ++ |
| L. J. | 12 | F | 92<br>T. 98.6 | 0.20 c.c.-0.095 mg./kg. | 10.0 | 108 | 114 | 130/75 | ++ |
| T. H. | 12 | F | 85<br>T. 98.6 | 0.20 c.c.-0.10 mg./kg. | 12.0 | 108 | 120 | 110/65 | ++ |
| J. G.* | 11 | M | 65<br>T. 98.0 | 0.17 c.c.-0.11 mg./kg. | 7.0 | 132 | 130 | 130/60 | ++ |
| *Children With Slight Elevation of Temperature* | | | | | | | | | |
| D. W.<br>Rheumatic fever | 8 | M | 49<br>T. 100.5 | 0.18 c.c.-0.15 mg./kg. | 8.0 | 112 | 114 | 99/50 | ++ |
| R. J.<br>Rheumatic fever | 11 | M | 59<br>T. 100.5 | 0.20 c.c.-0.15 mg./kg. | 12.0 | 114 | 120 | 90/50 | + |
| G. B.<br>Acute tonsillitis | 10 | M | 60<br>T. 99.8 | 0.20 c.c.-0.15 mg./kg. | 10.2 | 114 | 104 | 100/65 | ++ |

*This patient was very apprehensive and excited.

TABLE II

CHILDREN WITH SEPTAL DEFECT (VENTRICULAR) WITHOUT CYANOSIS OR PULMONARY STENOSIS

| NAME | AGE | SEX | WEIGHT (LB.) TEMPERATURE (° F.) | AMOUNT OF NaCN | CIRCULATION TIME (SECONDS) | PULSE BEFORE | PULSE AFTER | B. P. | INTENSITY OF REACTION |
|---|---|---|---|---|---|---|---|---|---|
| J. H. | 7 | M | 40 lb. T. 98.2 | 0.18 c.c.-0.20 mg./kg. | 12.0 | 98 | 100 | 85/50 | + |
| C. H. | 11 | M | 85 T. 98.6 | 0.20 c.c.-0.10 mg./kg. | 12.5 | 102 | 98 | 100/65 | + |
| G. N. | 16 | M | 150 T. 98.4 | 0.25 c.c.-0.075 mg./kg. | 13.0 | 82 | 88 | 110/70 | ++ |
| M. M. | 6 | M | 45 T. 98.0 | 0.15 c.c.-0.14 mg./kg. | 13.0 | 106 | 114 | 90/50 | ++ |
| C. M. | 5 | M | 40 T. 98.4 | 0.15 c.c.-0.16 mg./kg. | 10.0 | 114 | 118 | 85/60 | ++ |

TABLE III

TETRALOGY OF FALLOT

| NAME | AGE | SEX | WEIGHT (LB.) TEMPERATURE (° F.) | AMOUNT OF NaCN | CIRCULATION TIME (SECONDS) | PULSE BEFORE | PULSE AFTER | B. P. | INTENSITY OF REACTION |
|---|---|---|---|---|---|---|---|---|---|
| C. B. | 7 | M | 50 lb. T. 98.0 | 0.18 c.c.-0.16 mg./kg. | 3.8 | 112 | 100 | 85/60 | +++ |
| W. S. | 10 | M | 65 T. 98.4 | 0.18 c.c.-0.12 mg./kg. | 4.8 | 98 | 98 | 90/55 | ++ |
| M. H. | 13 | F | 85 T. 98.0 | 0.20 c.c.-0.11 mg./kg. | 4.0 | 86 | 90 | 100/65 | ++ |

obtained. This shortening of the circulation time in normal children as compared to adults may be due to the excitement incident to the procedure and the accompanying acceleration of the pulse rate. However, the shorter distance from the arm to the carotid artery in children as compared with adults is probably an even more important factor.

Using the same technique we have examined 5 children with congenital heart disease without morbus caeruleus. The circulation time for this group, most of whom were thought to have uncomplicated interventricular septal defects, averaged 12.1 seconds (Table II).

The clinical data regarding the three patients which we believe have patent interventricular septa with right-to-left shunt are summarized in Table III and in the case reports. None of these patients here described have been autopsied. However, the clinical diagnosis of tetralogy of Fallot was concurred in by three clinicians in each case.

### CASE REPORTS

CASE 1.—M. H., a white female, aged thirteen years, has had constant cyanosis since birth. The patient complained of marked dyspnea on exertion and attacks of dizziness and fainting. There was marked cyanosis of the lips, tongue, conjunctivae, and nail beds, with a dusky flush of the cheeks. There was moderate clubbing of the fingers. The heart on examination revealed slight enlargement to the right and left with a loud systolic murmur heard best in the third left interspace 2 cm. to the left of the sternum. The pulmonic second sound was accentuated. Fluoroscopy verified the slight enlargement and showed prominence of the pulmonary conus and heavy lung fields. There was only moderate pulsation of the conus and no movement of the hilum shadows. Electrocardiogram showed right axis deviation. Red blood cells numbered 6,000,000; whole blood viscosity was 6 (Hess viscosimeter); circulation time was 4.0 seconds—cyanide.

CASE 2.—W. S., a white male, aged ten years. Cyanosis was first noticed at the age of two years, and has been severe and constant since. Dyspnea and dizziness were present on exertion. There were several small hemoptyses. There was marked cyanosis of the nails, lips, tongue, and conjunctivae with marked clubbing of fingers. There was a loud systolic murmur to the left of the sternum in the second interspace; pulmonic second sound was accentuated. Fluoroscopy revealed slight enlargement to the right and left, with normal waistline and blunting of the apex. Electrocardiogram showed marked right axis deviation. Red blood cells numbered 6,200,000; whole blood viscosity was 6.5; circulation time was 4.8 seconds—cyanide.

CASE 3.—C. B., a white male, aged seven years, has had constant cyanosis since birth. Dyspnea has been of moderate degree. Cyanosis of lips, mucous membranes, conjunctivae, and nail beds was marked. The skin had a dusky appearance. Marked clubbing of toes and fingers was present. Heart was enlarged to right and left with loud harsh systolic murmur, loudest at the second left interspace. $P_2$ was diminished in intensity. Fluoroscopy revealed enlargement of moderate degree to both right and left with decreased radiovisibility of both aortic and pulmonic shadows and diminished pulsations in the region of the pulmonary conus. Electrocardiogram showed marked right axis deviation. Red blood cells numbered 7,000,000; blood viscosity was 7.2; circulation time was 3.8 seconds—cyanide.

We studied two additional patients with morbus caeruleus in whom it was impossible to elicit a reaction with the cyanide even to the point of doubling the calculated dose (one of the patients received 0.5 c.c. without any reaction). It was noticed that the blood viscosity was tremendously elevated in these two cases, being 9.0 and 10.6 respectively. The slowing of the flow consequent to the increased viscosity might afford an opportunity for diffusion and inactivation of the cyanide.

## DISCUSSION

Examination of the results shows that in the three cases exhibiting clinical evidence of patent septal defects with venous-arterial shunt the circulation time averaged 4.2 seconds, while in the control group the average value was 10.6 seconds. In one child with fever the circulation time was 8.0 seconds and in another who was apprehensive and crying the reaction occurred in 7.0 seconds. The three patients with the tetralogy of Fallot were calm and placid during the examination, and their lack of excitement made the rapid end point even more convincing and clean cut.

It seems clear that patients with increased blood viscosity, normal blood pressures, and normal pulse rates could not possibly have increased the velocity of the flow by 100 per cent. It is also obvious that a "short circuit" via the patent septum would eliminate the necessity of circulation through the lungs. Hence the stimulating drug need only pass directly from the right to the left ventricle and thence to the carotid sinus, shortening the pathway and giving an apparent increase in the velocity of flow.

In simple patency of the interventricular septum without increased right intraventricular pressure, we would not anticipate shortening of the circulation time as right-to-left shunting of the blood would not be expected. Thus only with pulmonary stenosis or other intrapulmonary lesion causing right ventricular hypertrophy and rise in the right intraventricular pressure plus septal defect would one anticipate a shortened circulation time. It seems clear that interauricular septal defects, patency of the foramen ovale, or patent ductus arteriosus would likewise reduce the circulation time if factors favoring a right-to-left shunt were present. We have so far had no opportunity to study such cases.

We have observed the cases with septal defects closely for a second respiratory response several seconds after the initial reaction which might be due to a portion of the cyanide traveling the long road through the lungs. In none of the cases was a second and delayed response noticed. The amount of cyanide passing through the lungs may have been too small to cause carotid sinus stimulation, or diffusion and inactivation of the cyanide may have been a factor in the failure to elicit a second response.

## SUMMARY AND CONCLUSIONS

1. In three cases of congenital heart disease with the clinical diagnosis of venous-arterial shunt, the circulation time averaged 4.2 seconds. This rapid circulation time is probably pathognomonic of right-to-left shunt.

2. The arm-to-carotid sinus circulation time of eleven normal children averaged 10.6 seconds with the sodium cyanide method of Robb and Weiss.

3. In five patients with acyanotic congenital heart disease, most of whom were thought to have uncomplicated interventricular septal defects, the average circulation time was 12.1 seconds.

4. It is recommended that the cyanide test be used as an aid in the diagnosis of a venous-arterial shunt in cases of congenital heart disease.

We are indebted to the pediatric department for affording us the opportunity of studying these cases.

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# A NEW APPARATUS FOR RECORDING HEART SOUNDS*

EDWARD W. HOLLINGSWORTH, M.D., LAWRENCE M. SORENSEN, AND ALBERT VAN DEN DRIESSCHE
HINES, ILL.

FOR the past two years we have been working with devices for the amplifying and recording of heart sounds. Our available equipment consisted of a No. 2 and a No. 3 mobile type Hindle electrocardiograph. After considerable experimenting it was found possible to arrange them so that both light fields could be focussed on one camera, that of the No. 3, and fairly well equalized. Two different leads, or one in duplicate, could be taken (Fig. 3*A*) and were apparently identical with those taken in the usual manner. A small amount of parallax was present.

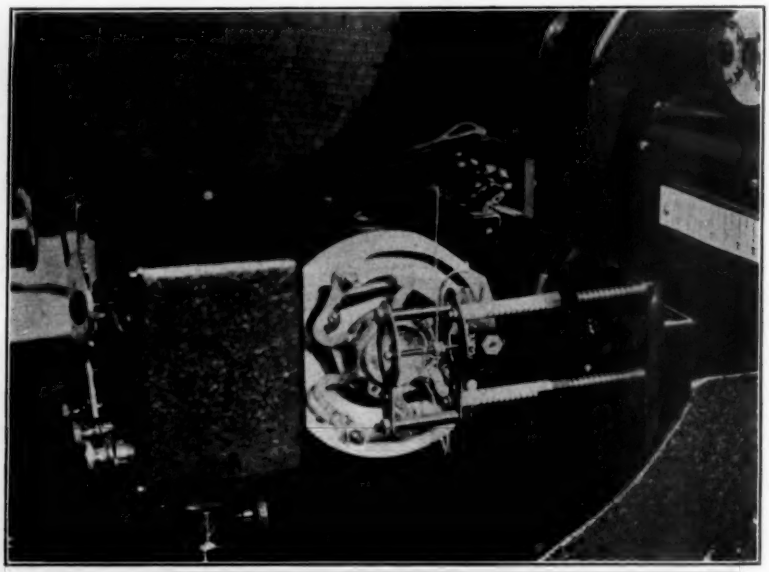

Fig. 1.—The recording unit.

Sound records were made by means of a hook-up, furnished by Mr. A. W. Krause of Northwestern University, and one of the electrocardiographic strings. The tracings obtained by us were not satisfactory and as considerable time was required for the setup the method was abandoned and a simpler one sought. One of us (L. M. S.) conceived the idea of using a radio loud speaker unit, the magnetic type being selected because of its responsiveness and light weight, no cone being used (Figs. 1 and 2). A thin metal rod or needle was attached directly to the moving coil and placed in the light field of one of the electrocardiographs so as to cast a shadow beside that of the string. Good focus was obtained at varying distances from the camera and the unit could be used with either of the machines.

*Published with the authority of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn.

An astatic crystal type microphone No. C. P. 104 gave good results. A 606 tube was used in the preamplifier (Fig. 2), extreme care being taken in the shielding

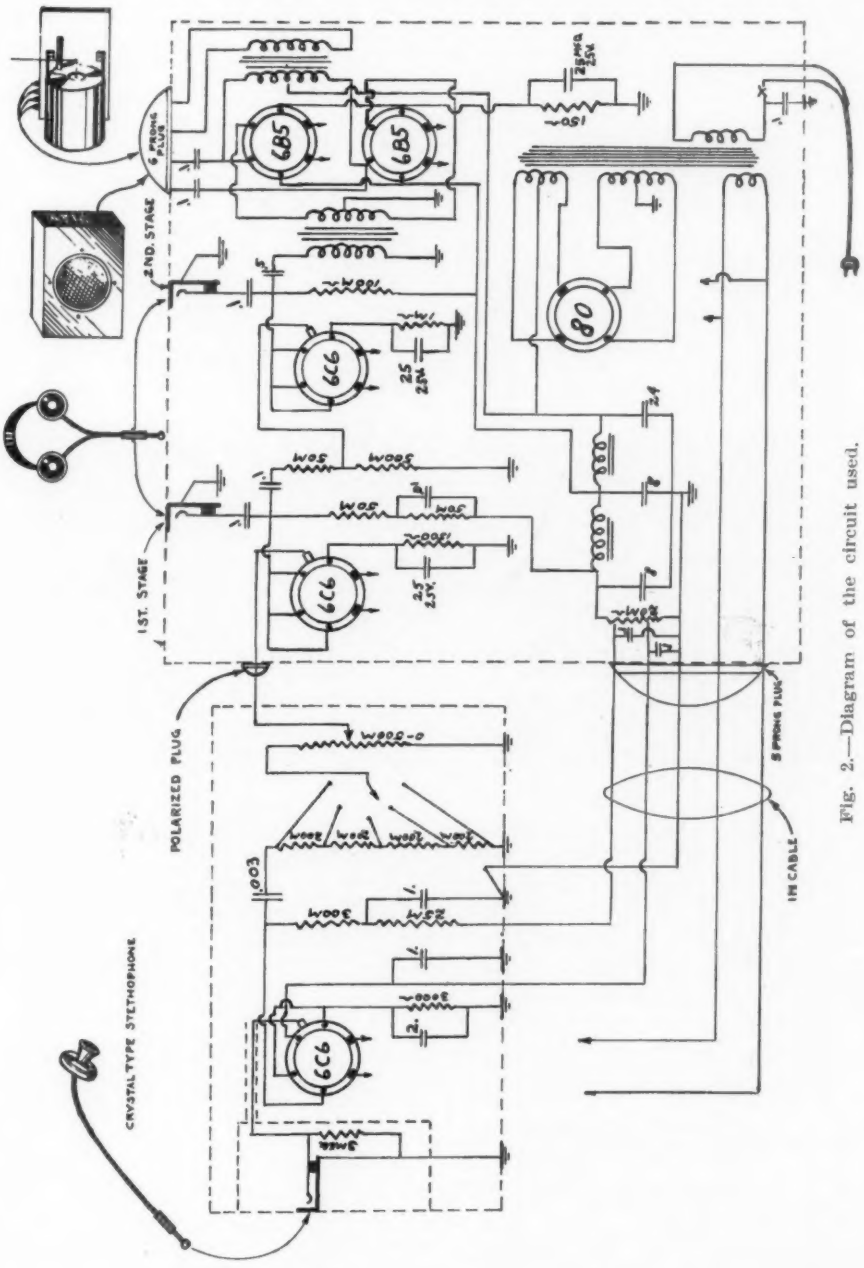


Fig. 2.—Diagram of the circuit used.

of the input because, due to high gain, A. C. hum was picked up. Hence, a metal cover was substituted for the bakelite on the microphone plug, a second shield being placed over the first, and then its jack, including the resistor, was shielded and shielded wire run to the grid of the tube.

A special attenuator with four fixed steps and a variable control to subdivide them is employed, and the output of this unit is fed into the main circuit through a shielded cord. There are two 6C6 tubes in the main amplifier with the suppressor and screen grid tied to the plate. They are resistance-coupled and feed two 6B5 tubes in push-pull. Shielding is also necessary in the input stages of this amplifier although not so important as in the preamplifier.

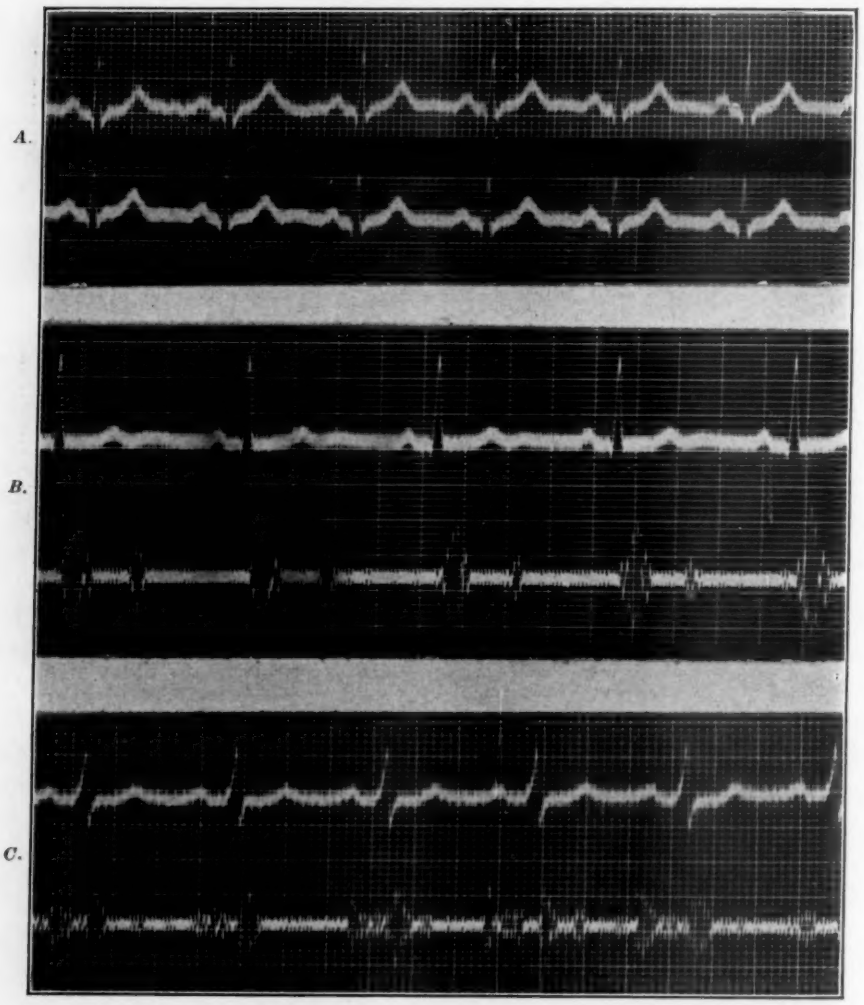


Fig. 3*A*.—Lead II taken simultaneously on No. 3 (upper tracing) and No. 2 (lower tracing) Hindle electrocardiographs. A small amount of parallax is present. The black area was made by the shadow of the shield used to separate the two light fields.

Fig. 3*B*.—Lead II and heart sounds from the apex of a patient with a normal heart.

Fig. 3*C*.—Lead II and sound tracing from the apex region of a patient with free aortic insufficiency, positive blood Wassermann reaction and 4 plus Kahn test, negative blood culture and signs suggesting mitral stenosis. A presystolic murmur is shown and was an important lead in establishing this diagnosis. Autopsy showed mitral stenosis and bacterial endocarditis of the aortic valve.

Headphones may be used in either first or second stage and a six-pronged socket is so arranged that one pair of contacts may be used for them, one for a magnetic or dynamic speaker, and the third for the recording apparatus. This

device may be used with any "shadow type" electrocardiograph with regulation bromide paper, the same time-lines serving for both sound and electrocardiographic records. The standard five-spoke or special single-spoke time wheel may be used.

Both Bowles and Ford type stethoscope object pieces have been tried but better tracings were obtained with the microphone itself applied directly to the chest wall. It was found that low frequency murmurs were more easily depicted than the higher pitched ones as has been the experience of other workers. Some attempt was made to cut out the lower frequencies but no satisfactory results were secured from the little work done.

Certain advantages seem apparent in the above apparatus over other devices in use. It is mobile and can be readily attached to or detached from the electro-

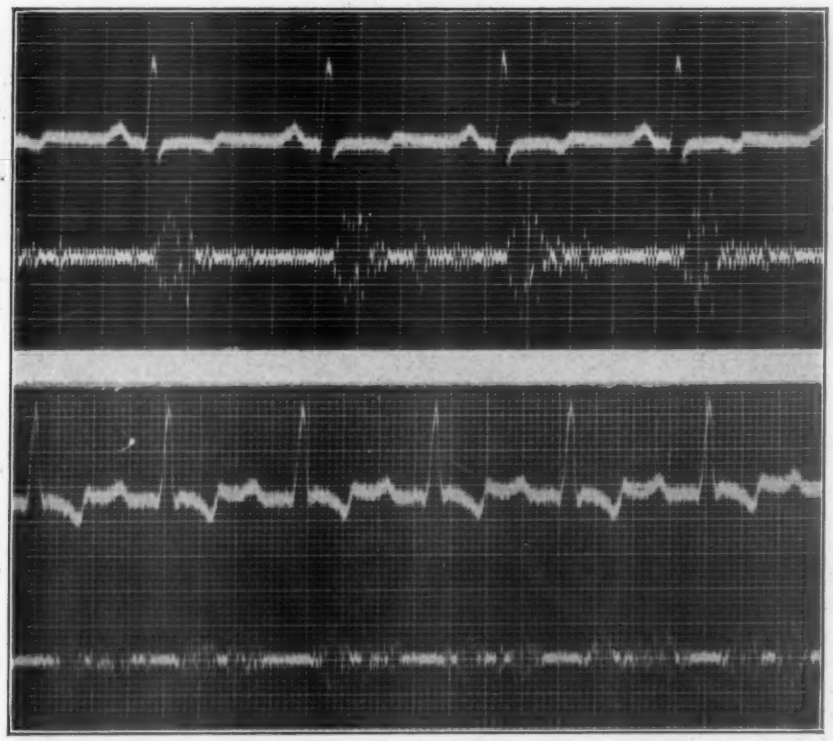


Fig. 4*A*.—Lead II and sound tracing from the third left interspace. Clinical diagnosis was syphilitic aortitis with well-marked double murmur.

Fig. 4*B*.—Lead II and sound tracing from second left interspace of a patient with syphilitic aortitis and unusually long diastolic murmur.

cardiograph. Since the sound record is a shadow, it is possible when the electrocardiogram is, and one set of time-lines is used for both.

## SUMMARY

A new apparatus for recording heart sounds is described, consisting essentially of an amplifier and magnetic radio speaker with a needle casting the shadow comprising the tracing attached directly to the moving coil. Advantages it is believed to possess over similar devices now in use are enumerated.

The authors wish to thank Dr. F. N. Wilson and Dr. Paul F. Barker of Ann Arbor for valuable suggestions.

# Department of Clinical Reports

## ACQUIRED INTERVENTRICULAR SEPTUM DEFECT

### Report of a Case

Dean F. Stanley, M.D.
Decatur, Ill.

AMONG the rare, but very interesting, complications of coronary thrombosis is an acquired defect in the interventricular septum produced by rupture through an infarct involving that structure. Altogether some twenty cases of the condition have been reported in the literature, of which the case to be reported is, as far as I have been able to find, the third in which the correct diagnosis has been made during life. Although it has been stated that rupture of the septum probably imposes no great additional burden on these hearts which usually are extensively involved by infarction, it was our impression that our patient was greatly shocked by the rupture, and that her clinical course was downhill thereafter.

#### CASE REPORT

Mrs. C. E. E., housewife, aged sixty-one years, was first seen in her home at 7:00 A.M. on April 8, 1936, by Dr. A. F. Goodyear. She had been well until the early morning of that day when she was awakened by upper epigastric pain radiating upward and to both arms. This was followed by severe and frequent vomiting. The heart was not enlarged to percussion, the tones were somewhat distant and no murmurs were heard. Temperature was 97.4° F., pulse 60, and the blood pressure was systolic 140, diastolic 86 mm. Morphine sulphate, ¼ grain, was given by subcutaneous injection with some relief of the substernal pain. The pain in the arms persisted for several hours thereafter. At 9:00 P.M. on April 9, 1936, the patient entered Decatur and Macon County Hospital with the diagnosis of suspected coronary thrombosis. Urinalysis at that time showed an amber, acid urine, sp. gr. 1.016, a trace of albumin, and no sugar. There were 10 to 15 pus cells to the high-power field, an occasional red blood cell and an occasional hyaline cast. Blood study showed a hemoglobin of 84 per cent (Sahli); red blood cells, 4,270,000; white blood cells, 9,800. A differential count gave 61 per cent of polymorphonuclears of which 3 per cent were band forms, 33 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophiles. Blood sugar was 130 mg.

The patient gradually improved until the evening of April 11, when following the giving of an enema for distention, and while she was on the bedpan, she was stricken with substernal pain and went into shock with sweating, cyanosis, and dyspnea. There developed at this time a loud, harsh, systolic murmur accompanied by a thrill, located in the fourth interspace just to the left of the sternal border. This persisted relatively unchanged until death. A pericardial friction rub was also heard at this time. Blood pressure was systolic 100, diastolic 60 mm. The patient was in a

precarious condition for two weeks following this episode with dyspnea, air hunger, vomiting, and exhaustion. The blood pressure fluctuated between 98/46 and 118/56

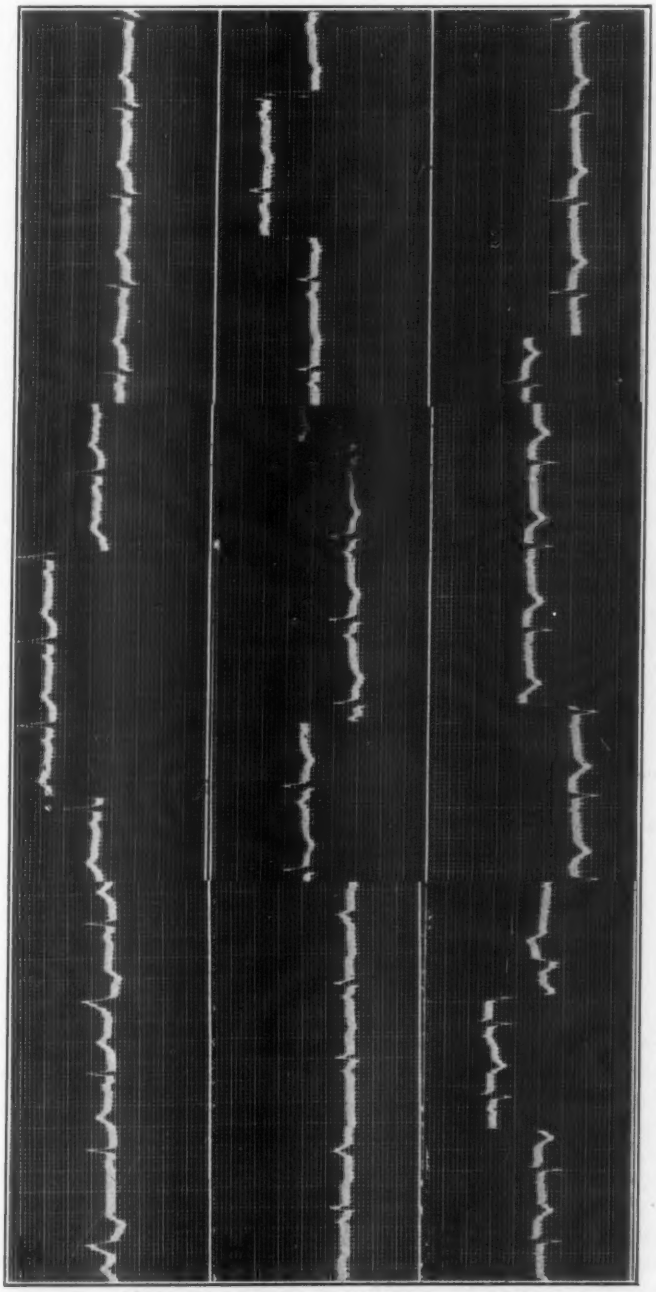


Fig. 1.—Serial electrocardiograms on patient. See text for description. *A*, tracings made April 24, 1936; *B*, tracings made May 5, 1936; and *C*, tracings made June 1, 1936.

during this period. Dr. M. E. Rose saw the patient in consultation on April 12 and was in attendance with Dr. Goodyear for ten weeks thereafter. The patient was first seen by the author on April 24 at which time an electrocardiogram was taken.

This showed low QRS complexes in all leads: cove-plane R-T intervals with a high take-off in Leads II and III; occasional ectopic beats, all from the same focus and apparently ventricular in origin: slight left ventricular predominance. A diagnosis of coronary thrombosis of the $T_3$ type was made. Other tracings were taken on May 5, 1936, and June 1, 1936, which showed the usual further changes characteristic of serial electrocardiograms taken on patients with acute coronary occlusion. On May 28, 1936, the following note was made on her chart by the author. "I wish to get in writing here my diagnosis of perforation through an infarct in the interventricular septum as a cause for the sudden development on April 11, 1936 of the loud systolic murmur and definite thrill to the left of the ensiform process."

After many vicissitudes with episodes that were interpreted as small infarctions from emboli involving lungs, brain, and kidneys, the patient left the hospital not substantially improved on July 30, 1936. At home she remained in bed under the care of a nurse. She showed evidence of increasing decompensation. Right hemiplegia developed and death occurred on Sept. 14, 1936.

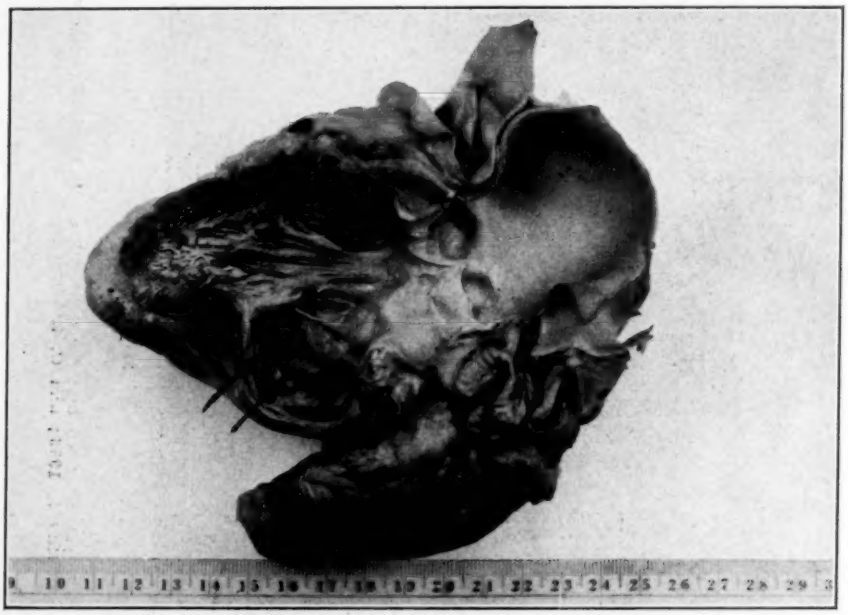

Fig. 2.—Photograph of heart of patient. Arrows point to the two perforations in the interventricular septum.

*Abstract of Autopsy Report.*—Dr. Perry J. Melnick, pathologist.

At autopsy the findings of cardiac decompensation were quite marked, and included pitting edema of the lower extremities, 2,000 c.c. of clear yellow fluid in the abdominal cavity, 100 c.c. of similar fluid in the pericardial sac, 3,500 c.c. and 1,000 c.c. of similar fluid in the right and left pleural cavities, respectively, which compressed both lungs, and passive congestion of the abdominal viscera. The important findings were in the heart. The heart weighed 350 gm. The left ventricle was in general 18 mm. thick, but the posterior wall of the left ventricle was reduced to a thickness of 3 to 4 mm. and was composed of firm whitish tissue—microscopically seen to be scar tissue—which bulged backward, forming an aneurysm. The adjacent one-half of the interventricular septum was similarly composed of a thin layer of firm scar tissue. Near the center of this scarred area in the septum was an oval hole 12 mm. in diameter with smooth edges, and just posterior to this large defect was

a smaller one 3 mm. in diameter. The right and left ventricles communicated through these openings. The remainder of the myocardium was soft and deep chocolate brown. The right ventricle was 8 mm. thick and the conus pulmonalis was very distinct. The valves were all unchanged, and the aorta above the valve was 80 mm. in circumference with only a few fatty and hyaline plaques in the intima.

In the right coronary artery about 2 cm. from the orifice there was a large calcific plaque which completely encircled the lumen and produced an almost complete stenosis. The remainder of the right coronary as well as the left coronary arteries had a moderate number of hyaline and calcific plaques.

Anatomical diagnosis: Ancient myomalacia, with aneurysmal bulging of the posterior part of the left ventricle of the heart, and of the adjacent one-half of the interventricular septum. Multiple (2) spontaneous perforations of the interventricular septum. Severe sclerosis of the proximal portion of the right coronary artery with marked stenosis of the lumen. Bilateral hydrothorax, hydropericardium, ascites, and anasarca. Chronic passive congestion of the lungs, liver, spleen, and gastrointestinal tract. Compression atelectasis of both lower pulmonary lobes. Moderate eccentric hypertrophy of the heart, especially of the right ventricle, with brown atrophy of the myocardium.

Since Sager[1] has reviewed the literature on perforation of the infarcted septum in coronary thrombosis and has very adequately discussed criteria for diagnosis and differential diagnosis, no useful purpose would be served by further discussion here. Since his article appeared, two other cases have been reported, those of Kepler, Berkman, and Barnes,[2] and Gross and Schwartz,[3] in neither of which, however, was the condition diagnosed ante mortem. Brunn and Sager made correct ante-mortem diagnoses in their cases, and the present is therefore, as far as we can determine, the third such case reported.

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3. Gross, Harry, and Schwartz, Sidney P.: A Case of Acquired Interventricular Septal Defect Associated With Long-Standing Congestive Heart Failure, Am. Heart J. 11: 626, 1936.

# Department of Reviews and Abstracts

## Selected Abstracts

**Radnai, P.: The Action of Acidity on the Heart Muscle.** Ztschr. f. Kreislaufforsch. **29**: 18, 1937.

The author found that therapeutic doses of ammonium chloride had no effect histologically on the heart muscle of the rabbit. Larger doses lead to degeneration and round cell infiltration.

It was found that in 3 out of 17 cases in man abnormalities in the electrocardiogram developed: in 2 an A-V block appeared and in a third an intraventricular block appeared. There is thus a risk of aggravating conduction disturbances with acid salt therapy in large doses.

L. N. K.

**de Boer, S., and Brouwer, A.: The Action of Hydroquinine, Hydroquinidine, Quinine P and Quinidine P on Heart Rate and Refractory Phase.** Ztschr. f. Kreislaufforsch. **29**: 52, 1937.

All these drugs cause an increase in heart rate and a prolongation of the refractory phase.

L. N. K.

**Scarff, R. W., and McGeorge, Murray: Experimental Renal Lesions and Blood-Pressure in Rabbits.** Brit. J. Exper. Path. **18**: 59, 1937.

Many workers have produced hypertension in experimental animals by means of a direct attack upon the kidneys while others, using the same or similar methods, have been unable to achieve the same results. The authors have studied the effect upon the blood pressure in rabbits of various forms of renal injury, including oxalate nephritis, unilateral and bilateral nephrectomy, trauma, ligation of ureters, and glomeruli embolism of inert material and killed material in previously sensitized animals. The blood pressure determinations were made by means of carotid loops prepared according to the method of van Leersum. The blood pressure of normal rabbits was determined to be a mean of 96 mm. in systolic pressure with a range of 74 to 120 mm. The blood pressure of the rabbits was carefully standardized over a period of at least two weeks before any of the procedures was carried out. In six rabbits, oxalate nephritis was produced by the injection of varying quantities of oxalate crystals intravenously. Unilateral nephrectomy was performed fourteen days prior to the oxalate injections in two of the animals. Simple embolism was produced in a group of rabbits previously subjected to unilateral nephrectomy, by injection of laked red blood corpuscles directly into the renal artery. Seven rabbits survived long enough to make satisfactory blood pressure studies. In one of the rabbits, the remaining kidney was removed, and in another the ureter was ligated. Killed streptococci were injected into the renal arteries of five previously sensitized rabbits.

Although in many of the animals considerable impairment of renal function was caused by these various procedures, in none was there found a significant rise in blood pressure.

E. A. H.

**Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys.** Brit. J. Surg. 24: 787, 1937.

Sympathectomy for relief of severe vasospastic states of the lower extremities has been successful for many years. However, it was not usually successful in the upper extremities until J. C. White pointed out that the conventional operations severed preganglionic fibers to the foot, whereas in the operation for the hand postganglionic fibers were cut. White showed that the failure of postganglionic section of the sympathetics to the hand was due to sensitization of the muscle of the vessel coat to adrenalin. He and his coworkers have recently published a series of cases of sympathectomies on the upper extremities of patients with vasospastic disorders, performed by preganglionic section. The results have been good—as good as those of the conventional operation in the lower extremities.

The study of the present authors is on the Rhesus monkey, in which the sympathetics have much the same anatomical arrangement as in man. Studies of skin temperature following heating of the body and following injection of adrenalin have been made. On 12 monkeys sympathectomies of the conventional, old type were performed in the upper extremity. In only one of these has a good degree of vasodilatation persisted, and in at least 2 the sympathectomized side was more sensitive to cold than was the normal side. Eleven of the 12 developed an adrenalin sensitivity about 10 times the normal, whereas one was about half as sensitive as the others. When the lumbosacral sympathetic chain was excised (2 animals—postganglionic section of lower extremities), the result was much the same. In 8 monkeys the thoracic chain was cut just above or below the third thoracic ganglion (preganglionic section). In none of these has the sympathectomized side constricted as much as in the case of the postganglionic sections. Adrenalin sensitivity is only about one-third as intense as after postganglionic section. The experimental data agree with the recent conclusions of White and his coworkers on the advisability of the new type of sympathectomy for vasospasm of the upper extremities.

H. M.

**Tannenberg, Joseph: The Rôle of Allergy in the Pathogenesis of Progressive Thrombosis, Especially in Regard to Changes in the Endothelial Lining of Large Peripheral Veins.** Arch. Path. 23: 501, 1937.

The author, in agreement with some and in contradiction to other authors, finds no conclusive evidence in favor of experimental thrombus formation by allergic processes, although he agrees that repeated injections of antigen can injure the vessels.

Twenty-four rabbits were used. Each animal was prepared by nine intravenous injections, over the course of three weeks, of some one antigen. Sheep serum and killed pneumococci and streptococci were used. From seven to eighteen days after the last of these injections the right jugular and femoral veins were made narrower by means of ligatures placed aseptically. The antigen (living or killed) was then injected into another vein and the animals were killed twenty-four hours later. The control animals were of two sorts: those fully prepared but receiving in all one dose of antigen. The jugular and femoral veins of the controls were constricted by ligature. Several sections of various veins were stained and studied. In a high percentage of the immunized rabbits (both those fully treated and the fully immunized controls) small inflammatory lesions were found in the pulmonary arteries and in the heart, and this occurred only once in 50 of those control animals which received a single injection only. This obviously does not imply that these lesions have allergic origin. None progressed to thrombosis.

What thrombi did appear appeared only near the points of constriction by ligature and were no more frequent in immunized than in nonimmunized controls, apparently indicating that the thrombi that appeared were of traumatic origin.

H. M.

**Freyberg, R. H.: Relation of Experimental Atherosclerosis to Diets Rich in Vegetable Protein.** Arch. Int. Med. **59**: 660, 1937.

Newburgh and Squier (1920) and Newburgh and Clarkson (1923) have shown previously that a diet rich in animal protein produces atherosclerosis in rabbits. Eight of 11 animals that were fed a diet containing 27 per cent animal protein for more than six months became atherosclerotic. The occurrence and extent of the sclerosis is roughly proportional to the duration of feeding of meat. It had also been shown that the cholesterol content of these diets was too small to be the cause of the atherosclerosis.

The present authors studied the effect on rabbits of feeding diets rich in proteins of vegetable origin. Diets containing 33 and 37.8 per cent of vegetable protein fed to twelve rabbits for as long as eleven months failed to produce atherosclerosis.

H. M.

**Grant, F.: Circulation in Pneumothorax.** Deutsches Arch. f. klin. Med. **178**: 670, 1936.

Forty patients in whom pneumothorax was performed for tuberculosis were studied. The pulse was found to be slightly slower following pneumothorax, and there was less sinus arrhythmia. Ventricular extrasystoles were produced in 8 cases. In all instances the electrocardiogram showed a right axis deviation due doubtlessly to a depression of the diaphragm. Occasionally there occurred reversible changes in the S-T and T-waves.

L. N. K.

**Nothhaas: The State of the Peripheral Circulation in Health and Disease.** Klin. Wchnschr. **15**: 778, 1936.

The author determined heat elimination of the right hand by a calorimeter. He found that the intracutaneous wheal produced by aolan caused a sharp decrease in heat elimination in the normal man (40 men of from twenty to fifty years of age). In 30 patients with gastric ulcers and 11 with bronchial asthma this stimulus was found to cause an increase in heat elimination in two-thirds of the cases. The other one-third showed a small decrease.

L. N. K.

**Jores, A.: The Rôle of the Hypophysis in High Blood Pressure, Especially in Essential Hypertension.** Klin. Wchnschr. **15**: 841, 1936.

Serum extracts of some patients with high blood pressure in which serum albumin had been precipitated by sulphosalicylic acid caused an increase in adrenal cortex of infantile mice. This resembles the response to corticotropic hormone. The two products resemble each other chemically also. This adrenal-cortex-stimulating substance was found in six cases of essential hypertension. It was not present in any of the eight examined patients with eclampsia and pregnancy toxemias. In four cases of renal high blood pressure and pneumonia, a noticeable cortical response was found in one and a slight one in the other three. It

was present in all six cases of apoplexy occurring in essential hypertension. The author believes that the results indicated that he has demonstrated that the hypophysis does play a rôle in hypertension.

L. N. K.

**Raab, W.: Excitability of the Vasomotor Centers in Man.** Klin. Wchnschr. **15**: 851, 1936.

Excitability of vasoconstrictor center increases with age in man when the blood pressure is normal. In acute nephritis the excitability is unchanged; in hypertension and arteriosclerosis it is markedly increased. Hypophysial material has no effect on excitability. Morphine and luminal decrease the excitability of the center in hypertensive patients. Carbon dioxide changes affect the vasomotor centers of old and established hypertensive patients much as anoxemia and local acidosis of the centers do in animals.

L. N. K.

**Flaxman, Nathan: Auricular Fibrillation.** J. A. M. A. **108**: 797, 1937.

Auricular fibrillation, the most common form of arrhythmia in hypertensive heart disease, occurred in 158 (25.3 per cent) of 623 patients with this disease. It definitely influenced the course of the disease in forty-four patients (27.8 per cent) in whom the rapid irregularity preceded and precipitated the congestive heart failure and led to an early death from this cause within one month after the onset in eight (18.1 per cent) of the forty-four patients. When the auricular fibrillation occurred after congestive heart failure had been present from one month to several years, it had no apparent influence on the course of the disease except in relation to the cause of death and the comparative absence of additional occurrences common to appear in hypertensive patients.

AUTHOR.

**Klisiecki, A., and Flek, S.: The Circulation in the Coronary Arteries of the Heart.**

**I. The Minute Volume Flow.** Ztschr. f. Biol. **97**: 7, 1936.

In dogs weighing 8 to 25 kilograms the flow in the coronary sinus was found to be 100 c.c. per 100 gm. heart per min. on the average. The size of the coronary arteries depends on the aortic pressure, the state of contraction of the heart muscle and the tone of the coronary vessels. Enlargement of the coronary vessels by elevated arterial pressure or decreased tone accompanying anoxemia increases the coronary flow.

**II. The Movement of Blood in the Coronary Arteries.** Ztschr. f. Biol. **97**: 12, 1936.

The rate of flow in the coronary artery at normal aortic pressure and heart rate is constant. When the arterial pressure is high and the rate slow, the flow is slower during systole than diastole. The contracting heart offers resistance to flow, and, when powerful enough, it stops flow entirely. Yet when contraction is increased following elevation in pressure, the minute volume is increased, the increase in flow during diastole compensating for the decrease during systole. A systolic acceleration of flow (such as described by Hochrein) occurs only when the coronary vessels constrict.

**III. Movement of Blood in the Coronary Sinus.** Ztschr. f. Biol. **97**: 19, 1936.

Flow in the coronary sinus depends on pressure and the ventricular contraction pressure. Changes in the right auricle have no effect. During ventricular

systole, there is an acceleration of flow. Slowing the heart decreases flow in the coronary sinus as the pressure within it falls during the long pauses. The heart has a massaging action on this flow.

**IV. The Problem of Vasomotor Nerves—Action of Adrenalin.** Ztschr. f. Biol. 97: 23, 1936.

There is a proportionality between the increase in aortic pressure and coronary flow. Soon after adrenalin one finds a decrease in flow when aortic pressure does not change and the heart does not accelerate. The so-called coronary dilator action of adrenalin is due to an increase in mechanical factors which accelerate coronary flow.

**V. Action of Vagi, Pilocarpine and Carotid Sinus Reflex on the Coronary Flow.** Ztschr. f. Biol. 97: 34, 1936.

The decrease in flow following vagus stimulation is due to a decrease in cardiac contraction and a fall in blood pressure. When arterial pressure is prevented from falling, an increase in coronary flow is found. The coronary vessels appear to be dilated by the vagus. Pilocarpine causes an increase in coronary flow when the heart is at a standstill. The carotid sinus reflex affects the coronary flow secondarily by its effect on the mechanical factors controlling coronary flow.

L. N. K.

**Coburn, Alvin F., and Moore, Lucile V.: The Independence of Chorea and Rheumatic Activity.** Am. J. M. Sc. 193: 1, 1937.

One-half of the cases of chorea under observation occurred in nonrheumatic subjects.

Approximately one-fourth of the cases of chorea occurred in quiescent rheumatic subjects.

Approximately one-fourth of the cases of chorea occurred during active rheumatism.

Uncomplicated chorea is accompanied by normal blood sedimentation rates.

Chorea per se does not suffice for the recognition of the rheumatic subject nor for the diagnosis of rheumatic activity.

AUTHOR.

**Gross, Louis, and Friedberg, Charles K.: Lesions of the Cardiac Valves in Rheumatic Fever.** Am. J. Path. 12: 855, 1936.

There are described the incidence and gross and microscopic appearances of lesions in the valves, valve pockets, and chordae tendineae occurring in 97 cases of rheumatic fever. These cases are divided into six clinical groups which represent various courses taken by this disease. It is shown that each group presents certain gross and microscopic features which bear a relation to the clinical grouping. Anatomical evidence is presented which suggests that the course taken by the disease as well as the response of the tissue may be determined by the relative state of immunity. This does not, however, imply that rheumatic fever is primarily an allergic disease. New macroscopic and microscopic data are presented on the development of the rheumatic lesions in the valves, and a discussion is given of the factors which determine the spread of infection, the localization of the verrucous and other lesions, the extent of the valvular damage and the pathogenesis of the characteristic deformities of the valvular apparatus. Certain stigmas of the

rheumatic process occurring in completely healed valves are described. These supply additional data which are of value in elucidating the pathogenesis of other cardiac lesions. A description is also given of the changes which take place in nonrheumatic valves during the first eight decades of life.

AUTHOR.

**Page, Irvine H., and Heuer, George J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots.** Arch. Int. Med. 59: 245, 1937.

Evidence of varied nature indicates that, as part of a more generalized vasoconstriction, vessels of the splanchnic area are narrowed in patients suffering from essential or malignant hypertension. Since no contraindications are known for reduction of the arterial pressure in such patients and there is no known medical treatment of more than temporary value, it appears to be justified to attempt to abolish the extrinsic vasomotor control of this area by section of the anterior nerve roots with the hope of reducing the arterial pressure. It has seemed desirable also to learn more of the part played by the nervous system in the genesis of hypertension. To this end seventeen patients have been subjected to the operation of section of the anterior nerve roots.

No attempt was made to select patients in whom in our opinion a favorable outcome might be anticipated. Six patients showed benign involvement of long duration, three of them with moderate vascular changes and three with severe changes. Six were young women with signs and symptoms of the "hypertensive diencephalic syndrome." Five suffered from highly malignant hypertension. The results of operation are therefore not comparable except within the subgroups.

While the ultimate effect of this operation on the natural course of hypertension cannot be foretold, from a study of these patients for periods of from eight to thirty-seven months after operation, the following results may be listed: (a) Three patients in whom the disease was severe but still benign and without advanced vascular change responded well. (b) One of three patients with more advanced involvement of long standing, with marked sclerotic but benign vascular changes, responded favorably. The headaches were relieved in the second and third cases, but the progress of the disease was unchecked. (c) Six young patients exhibiting the "hypertensive diencephalic syndrome" appeared benefited. (d) Three of those suffering from highly malignant hypertension were unaided by the operation, and two appeared to be improved. The favorable responses have been a marked, prolonged lowering of the arterial pressure, the remission of such symptoms as headache, pressure in the head and easy fatigability and marked improvement in the disposition. Other evidence of improvement in some of the patients has been relaxation of the spasm of the arterioles in the retina (eleven cases), absorption of exudate (two cases), disappearance of papilledema (three cases), and secondary glaucoma (one case), slight reduction in the size of the cardiac shadow in the roentgenograms (eight cases), and reversal of the T-wave from the inverted to the upright position in Lead I (two cases). There has been a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most, but not all, patients. Judgment must therefore be reserved as to the ultimate effects of the operation on the natural history of the disease.

Although marked anatomical change was present in the vessels of some of the patients, this did not prevent a marked fall in the arterial pressure, which persisted long after the patient had recovered from the immediate effects of the operation. This demonstrates that anatomical changes in the vessels do not account for the persistence of hypertension.

Renal efficiency, as measured by the urea clearance and the ability to concentrate urine, was unchanged either by the partial denervation of the kidneys, which resulted from the operation or from the fall in blood pressure.

In those patients exhibiting the "hypertensive diencephalic syndrome," a marked lowering of the blood pressure did not cause it to disappear. If this syndrome is the somatic expression of irritation of vegetative centers in the brain stem and is not abolished by a reduction of the arterial pressure, it is probably not caused by elevation of the arterial pressure.

The operation of laminectomy does not of itself reduce the arterial pressure for more than several weeks. Transverse myelitis at the eleventh thoracic segment reduces it for prolonged periods (one patient was studied for nine months). These observations, with those concerning the effect of section of the anterior spinal nerve roots on the arterial blood pressure, suggest that the nervous system plays some part in the genesis of hypertension.

Although the operation has markedly improved the clinical condition of many of the patients studied for periods up to two and one-half years, its ultimate value in the treatment of hypertension has not been established.

AUTHOR.

**Adson, A. W., and Allen, E. V.: Essential Hypertension: General Considerations and Report of Results of Treatment by Extensive Resection of Sympathetic Nerves and Partial Resection of Both Suprarenal Glands.** Proc. Inter-State Post Grad. Med. A. North America, 181-191, 1936.

Essential hypertension is a serious disease which seems to account for the deaths of about 23 per cent of all patients who are older than fifty years. Medical treatment is far from satisfactory in many instances. The idea that it is dangerous to lower the blood pressure in essential hypertension has been definitely disproved. The elevation of the blood pressure in essential hypertension is produced by an increased resistance to the flow of blood through the peripheral arterioles. The impediment offered to the flow of blood through the peripheral system in essential hypertension results either from functional changes, that is, vasospasm, or from organic changes, or from a combination of both.

Surgical treatment which is an attempt to diminish arteriolar tone in hypertension has been carried out in a group of patients whose hypertension was progressive and not satisfactorily controlled by medical treatment. The operation performed is a bilateral two-stage resection of the splanchnic nerves, the upper lumbar sympathetic chain and partial suprarenalectomy. The results vary from extremely good to extremely poor. If the blood pressure responds poorly preoperatively to rest, intravenous injection of pentothal sodium, administration of sodium amytal or sodium nitrite, the results of operation are invariably poor. If the blood pressure responds satisfactorily preoperatively to the measures noted, the results of operation are usually but not uniformly good. Patients are benefited symptomatically in a higher percentage of the instances than the blood pressure is satisfactorily influenced. When the blood pressure is satisfactorily reduced by operation, symptoms such as headache and pain in the left thorax are almost uniformly relieved, retinitis may disappear, narrowing and apparent sclerosis of the retinal arteries may be greatly minimized, transverse diameter of the heart may decrease, inverted T-waves in the electrocardiogram may become upright, albumin may disappear from the urine, and the renal function may be improved. As a result of the operation mentioned, the sweating function of the lower extremities is lost and the cutaneous temperature in this region is increased. The menstrual cycle and child-bearing function of the female are not disturbed. Sexual functions and ability of the male are not significantly impaired although ejaculation may not occur with orgasm. Orthostatic hypotension and

tachycardia are commonly noted following operation, but these disappear gradually. Although the interval since the operations have been performed is still comparatively short, there is evidence to justify an opinion that extensive subdiaphragmatic sympathectomy has been of value in reducing the blood pressure in essential hypertension.

AUTHOR.

**Kramer, David W.: The Use of Acetyl-β-Methylcholine Chloride by Iontophoresis in Peripheral Vascular Diseases.** Am. J. M. Sc. **193**: 405, 1937.

Acetyl-β-methylcholine chloride (mecholyl) is recognized by investigators as the most desirable preparation of the choline group for peripheral vascular disease.

Iontophoresis, or ionization, is the more direct and logical method of administering it in vascular disturbances. It is simple and practical.

In a series of 30 patients observed in the course of over 350 treatments, there were no serious untoward effects. Twenty-two patients (73 per cent) were benefited, 3 were helped only temporarily and were added to the 5 failures, giving a total of 8 (27 per cent).

The best results were obtained in the vasospastic group, 87 per cent responding favorable and excellently in the small phlebitis series; the diabetic cases showed a 65 per cent favorable response and the Buerger disease group 55 per cent.

Symptomatically, mecholyl had a decided influence upon fatigue and cramps regardless of the underlying lesions. It did not control the pain so readily, particularly in the diabetic and thromboangiitis groups.

The results of these observations evidently concur with the findings of those who investigated the pharmacological and physiological properties of acetyl-β-methylcholine chloride and suggested that it had possibilities in the treatment of peripheral vascular diseases. While it does not cure, mecholyl undoubtedly does give relief in many cases by improving and increasing peripheral circulatory function.

AUTHOR.

**Moissejew, S.: Dynamics of the Korotkow Sounds During Application of Warmth to Different Regions of the Body.** Ztschr. f. Kreislaufforsch. **29**: 78, 1937.

In many of 97 observations of blood pressure taken by the auscultatory method during application of heat to various portions of the body, it was noticed that the Korotkow sounds grew very weak (32 cases) or disappeared entirely (21 cases) for a short and variable period of time. The source of heat or the site of application, made little difference except that when larger areas, such as the whole back, were exposed to heat, the sounds were more likely to disappear completely. The change in the sounds occurs after approximately fifteen minutes of heating. The source of heat was, in most of the observations, an infra-red lamp, in a few, hot-water bottles, and in others, a current of hot air.

The author attributes the decrease in intensity of sound to increase in degree of contraction of the smooth muscle of the artery walls. This follows to a certain extent the reasoning of Janowsky. He concludes that on warming the body or parts thereof, a histamine-like substance is released, which stimulates the parasympathetic nerve endings and increases the tone of the large arteries. Unfortunately, records of the frequency of the sounds—records which might have given some information as to changes in elastic state or tone—were not taken. The conclusion drawn seems in this light unjustifiable, but recognition of the phenomenon is of considerable importance.

J. M. S.

**Chiari, H.: Concerning the Pathology of Peripheral Vessels.** Wien. klin. Wchnschr. **50**: 395, 1937.

The title is misleading in that remarks are confined entirely to the arteriovenous connections known as glomeri and tumors of these. The successive steps in their recognition and description are clearly and concisely reviewed, an equally clear and brief description of the current studies of microscopic anatomy is given, and the theories advanced as to their function are presented. The author then describes the occurrence of glomus tumors (angio-neuro-myoma) of which he has seen thirty-four cases. They usually occur in the fingers or somewhere on the upper extremity (21 instances) and give rise to pain, burning, and local heat. Because of the local elevation of temperature in these tumors which may be considered as pathologically enlarged glomeri, the author believes that the function of the glomus is one of heat regulation, as first suggested by Hoyer, rather than a regulator of blood pressure and cardiac work.

J. M. S.

**Allen, E. V.: The Peripheral Arteries in Raynaud's Disease: An Arteriographic Study of Living Subjects.** Proc. Staff Meet. Mayo Clin. **12**: 187, 1937.

The digital arteries of most patients with Raynaud's disease usually are not filled normally in arteriograms. Two common findings in the arteriograms in such cases are absence of filling of the distal parts of digital arteries and diminished caliber of such arteries. Arteriograms of asthenic individuals who do not have Raynaud's disease may reveal the same changes that the arteriograms in most cases of Raynaud's disease do. Some patients with Raynaud's disease, however, have normal arteriograms.

Cervicothoracic sympathetic ganglionectomy for Raynaud's disease may or may not produce normal filling of digital arteries which did not fill normally before operation. Evidence of intrinsic arterial disease manifested by sudden interruption of the lumen was observed in only two digital arteries and is therefore considered a finding of questionable importance. From an arteriographic standpoint, the digital arteries are not significantly diseased in an organic way in Raynaud's disease. If a "local fault" is responsible for Raynaud's disease, it does not appear in arteriograms as an organic one. Nevertheless, arteriography does not exclude such a "local fault" in Raynaud's disease since the arteriograms reveal changes in only the lumina of the arteries.

AUTHOR.

**Roesler, Hugo: A Roentgenological Study of the Heart Size in Athletes.** Am. J. Roentgenol. **36**: 849, 1936.

Four cases are reported and it is demonstrated (1) that the heart in healthy athletes may occasionally reach a size which justifies the diagnosis of slight enlargement and (2) that a diminution may take place after cessation of training.

Rautmann's concept of tests of speed and tests of endurance is given in relation to a possible cardiac response. Kirch's anatomical studies on the hearts of athletes are cited and critically analyzed.

AUTHOR.

**Sgalitzer, M., and Demel, R.: Differentiation Between Functional and Organic Diseases of the Peripheral Arteries by Roentgen Ray Studies.** Wien. klin. Wchnschr. **50**: 319, 1937.

The differential diagnosis between the several organic diseases of arteries can often be made with considerable accuracy by injecting opaque fluids into arteries.

"Primary arteriosclerosis" begins with a widening of the arterial lumen and eventually exhibits very irregular narrowing. Endarteritis obliterans and Buerger's disease begin with smooth regular narrowing which slowly progresses. The boundaries of the opaque medium are smooth and clear. Embolic closures of arterial lumina give rise to sharp shadows with a border convex proximally where the filling of the lumen ends abruptly. Spasm of the arteries is often recognizable by the concentric narrowing and by the smooth lance-form end of the shadow. The most important means of distinguishing organic from spastic disease arises, however, from the observation that dilatation of the arteries and arterioles takes place almost immediately after the injection of the solutions of organic iodides such as uroselectan. The authors' procedure has, therefore, been to follow the first injection by a second in ten minutes, to take films after each injection and compare the width of the arterial lumina in the two series of photographs. If the diameter of the vessels is different in the two pictures, the amount of widening in the second is a measure of the degree of spasm which existed. The method is said to be especially useful in distinguishing the relative degree of spasm and of organic disease in cases in which the two are combined. In addition, the authors state that therapeutic effects of release of spasm by the iodide solution have been observed to have a beneficial effect for as long as Leriche's operation upon the nerve supply to the arteries.

J. M. S.

**Pearson, Gertrude E. G.: A Note on the Calcium Aspirin Therapy of Chorea.** Canad. M. A. J. **36**: 516, 1937.

Calcium and aspirin were used in 23 cases of Sydenham's chorea with marked clinical improvement and a shortening of the average duration of the chorea.

Spinal fluid calcium estimations in 23 cases of chorea showed that there was no minimum figure below which chorea occurred. Variations in the calcium level in the spinal fluid were found ranging from 2.6 to 6.4 mg. per cent during the attack of chorea and after the chorea had subsided still ranging from 2.8 to 6.6.

With calcium and aspirin 17 cases of chorea showed an increase in the calcium of the spinal fluid, with a disappearance of the chorea; 6 cases showed a decrease in the spinal fluid calcium, also with a disappearance of the chorea. Many of the cases showing an increase later showed a decrease to the former level or below it, with no return of the chorea.

Some patients returned to the hospital several months after discharge with a recurrence of chorea, although the level of the spinal fluid calcium remained the same, or was higher than on discharge.

AUTHOR.

**Müller, E. A.: The Action of Cardiozol and the Respiration and Metabolism in Pernoctonnarcosis.** Med. Klin. **32**: 495, 1936.

The author states that cardiozol in the narcotized dog relieves narcosis, increases both respiration and metabolism and improves the state of both the respiratory and cardiac centers.

L. N. K.

# Books Received

DIGITALISFIBEL FÜR DEN ARZT. By Dr. Ernst Edens (Düsseldorf). Julius Springer, Berlin, 1937. 39 pages. Price, R.M. 1.80.

LA RADIOKYMOGRAPHIE DU COEUR ET DES VAISSEAUX. By Drs. Émile Bordet and H. Fischgold. Masson et Cie., Paris, 1937. 134 pages with 66 illustrations. Price, 30 fr.

MALADIE HYPERTENSIVE ET SYNDROMES D'HYPERTENSION. By Dr. A. Dumas. Masson et Cie., Paris, 1937. 136 pages. Price, 22 fr.

QUELQUES VÉRITÉS PREMIÈRES (OU SOI-DISANT TELLES) EN PATHOLOGIE CARDIO-VASCULAIRE. By Dr. E. Donzelot. Masson et Cie., Paris, 1937. 82 pages. Price, 24 fr.

A PATOLOGIA DA CIRCULAÇÃO CORONÁRIA: PROBLEMA DA ANGINA PECTORIS, INFARTO DO MIOCARDIO, SINDROMA DE ADAMS-STOKES. By Prof. Eduardo Coelho. Livraria Bertrand, Lisbon, 1937. 164 pages.

ESTUDIO FUNCIONAL DEL HIGADO AFECTADO POR EL ESTANCAMIENTO SANGUINEO EN LAS CARDIOPATIAS. Thesis by Severo R. Amuchástegui. Imprenta de la Universidad Nacional de Córdoba, 1936. 166 pages.

ROENTGENKIMOGRAFÍA CONCÉNTRICA. By Dr. Alberto C. Morelli. Montevideo, 1936. 34 pages and 34 plates.